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(71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(72) Inventor: GORMAN, Daniel, M.; 6371 Central Avenue, Newark, CA 94560 (US).

(74) Agent: ZARADIC, Sandy; Schering-Plough Corporation, Patent Department, K-6-1, 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

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(54) Title: MAMMALIAN RECEPTOR PROTEINS; RELATED REAGENTS AND METHODS

(57) Abstract: Nucleic acids encoding mammalian, e.g., primate, receptors, purified receptor proteins and fragments thereof. Antibodies, both polyclonal and monoclonal, are also provided. Methods of using the compositions for both diagnostic and therapeutic utilities are described.

MAMMALIAN RECEPTOR PROTEINS; RELATED REAGENTS AND METHODS

FIELD OF THE INVENTION

The present invention relates to compositions and methods for affecting mammalian physiology, including immune system function. In particular, it provides methods to regulate development and/or the immune system. Diagnostic and therapeutic uses of these materials are also disclosed.

BACKGROUND OF THE INVENTION

Recombinant DNA technology refers generally to techniques of integrating genetic information from a donor source into vectors for subsequent processing, such as through introduction into a host, whereby the transferred genetic information is copied and/or expressed in the new environment. Commonly, the genetic information exists in the form of complementary DNA (cDNA) derived from messenger RNA (mRNA) coding for a desired protein product. The carrier is frequently a plasmid having the capacity to incorporate cDNA for later replication in a host and, in some cases, actually to control expression of the cDNA and thereby direct synthesis of the encoded product in the host. See, e.g., Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.) vols. 1-3, CSH Press, NY.

For some time, it has been known that the mammalian immune response is based on a series of complex cellular interactions, called the "immune network". Recent research has provided new insights into the inner workings of this network. While it remains clear that much of the immune response does, in fact, revolve around the network-like interactions of lymphocytes, macrophages, granulocytes, and other cells, immunologists now generally hold the opinion that soluble proteins, known as lymphokines, cytokines, or monokines, play critical roles in controlling these cellular interactions. Thus, there is considerable interest in the isolation, characterization, and mechanisms of action of cell modulatory factors, an understanding of which will lead to significant advancements in the diagnosis and therapy of numerous medical abnormalities, e.g., immune system disorders.

The immune system of vertebrates consists of a number of organs and several different cell types. Two major cell types include the myeloid and lymphoid lineages. Among the lymphoid cell lineage are B cells, which were originally characterized as differentiating in fetal liver or adult bone marrow, and T cells, which were originally characterized as differentiating in the thymus. See, e.g., Paul (ed. 1998) Fundamental Immunology (4th ed.) Raven Press, New York; and Thomson (ed. 1994) The Cytokine Handbook 2d ed., Academic Press, San Diego. Lymphokines apparently mediate cellular activities in a variety of ways. They have been shown to support the proliferation, growth, and/or differentiation of cells, e.g., pluripotential hematopoietic stem cells, into vast numbers of progenitors comprising diverse cellular lineages which make up a complex immune system. Proper and balanced interactions between the cellular components are necessary for a healthy immune response. The different cellular lineages often respond in a different manner when lymphokines are administered in conjunction with other agents.

Cell lineages especially important to the immune response include two classes of lymphocytes: B-cells, which can produce and secrete immunoglobulins (proteins with the capability of recognizing and binding to foreign matter to effect its removal), and T-cells of various subsets that secrete lymphokines and induce or suppress the B-cells and various other cells (including other T-cells) making up the immune network. These lymphocytes interact with many other cell types.

Research to better understand and treat various immune disorders has been hampered by the general inability to maintain cells of the immune system in vitro. Immunologists have discovered that culturing many of these cells can be accomplished through the use of T-cell and other cell supernatants, which contain various growth factors, including many of the lymphokines.

Various growth and regulatory factors exist which modulate morphogenetic development. And many receptors for cytokines are also known. Often there are at least two critical subunits in the functional receptor. See, e.g., Gonda and D'Andrea (1997) Blood 89:355-369; Presky, et al. (1996) Proc. Nat'l Acad. Sci. USA 93:14002-14007; Drachman and Kaushansky (1995) Curr. Opin. Hematol. 2:22-28; Theze (1994) Eur. Cytokine Netw. 5:353-368; and Lemmon and Schlessinger (1994) Trends Biochem. Sci. 19:459-463.

From the foregoing, it is evident that the discovery and development of new soluble proteins and their receptors, including ones similar to lymphokines, should contribute to new therapies for a wide range of degenerative or abnormal conditions which directly or indirectly involve development, differentiation, or function, e.g., of the

immune system and/or hematopoietic cells. In particular, the discovery and understanding of novel receptors for lymphokine-like molecules which enhance or potentiate the beneficial activities of other lymphokines would be highly advantageous. However, the lack of understanding of how the immune system is regulated or differentiates has blocked the ability to advantageously modulate the normal defensive mechanisms to biological challenges. Medical conditions characterized by abnormal or inappropriate regulation of the development or physiology of relevant cells thus remain unmanageable. The discovery and characterization of specific cytokines and their receptors will contribute to the development of therapies for a broad range of degenerative or other conditions which affect the immune system, hematopoietic cells, as well as other cell types. The present invention provides new receptors for ligands exhibiting similarity to cytokine like compositions and related compounds, and methods for their use.

SUMMARY OF THE INVENTION

The present invention is directed to novel receptors related to cytokine receptors, e.g., primate, cytokine receptor like molecular structures, designated DNAX Cytokine Receptor Subunits (DCRS), and their biological activities. In particular, it provides description of various subunits, designated DCRS6, DCRS7, DCRS8, DCRS9, and DCRS10. Primate, e.g, human, and rodent, e.g., mouse, embodiments of the various subunits are provided. It includes nucleic acids coding for the polypeptides themselves and methods for their production and use. The nucleic acids of the invention are characterized, in part, by their homology to cloned complementary DNA (cDNA) sequences enclosed herein.

The present invention provides a composition of matter selected from: a substantially pure or recombinant polypeptide comprising at least three distinct nonoverlapping segments of at least four amino acids identical to segments of SEQ ID NO: 2, 5, 8, 11, 23, or 26; a substantially pure or recombinant polypeptide comprising at least three distinct nonoverlapping segments of at least four amino acids identical to segments of SEQ ID NO: 14; a substantially pure or recombinant polypeptide comprising at least two distinct nonoverlapping segments of at least five amino acids identical to segments of SEQ ID NO: 14; a natural sequence DCRS8 comprising mature SEQ ID NO: 14; a fusion polypeptide comprising DCRS8 sequence; a substantially pure or recombinant polypeptide comprising at least three distinct nonoverlapping segments of at least four amino acids identical to segments of SEQ ID NO: 17 or 20; a substantially pure or recombinant polypeptide comprising at least two distinct nonoverlapping segments of at least five amino acids identical to segments of SEQ ID NO: 17 or 20; a natural

sequence DCRS9 comprising mature SEQ ID NO: 17 or 20; or a fusion polypeptide comprising DCRS9 sequence. Preferably, wherein the distinct nonoverlapping segments of identity include: one of at least eight amino acids; one of at least four amino acids and a second of at least five amino acids; at least three segments of at least four, five, and six amino acids, or one of at least twelve amino acids. In other embodiments, the: polypeptide: comprises a mature sequence of Tables 1, 2, 3, 4, or 5; is an unglycosylated form of DCRS8 or DCRS9; is from a primate, such as a human; comprises at least seventeen amino acids of SEQ ID NO: 14 or 17; exhibits at least four nonoverlapping segments of at least seven amino acids of SEQ ID NO: 14 or 17; is a natural allelic variant of DCRS8 or DCRS9; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a primate DCRS8 or DCRS9; is glycosylated; has a molecular weight of at least 30 kD with natural glycosylation; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence.

The invention further embraces a composition comprising: a substantially pure DCRS8 or DCRS9 and another cytokine receptor family member; a sterile DCRS8 or DCRS9 polypeptide; the DCRS8 or DCRS9 polypeptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration. Additional embodiments include a polypeptide comprising: mature protein sequence of Tables 1, 2, 3, 4, or 5; a detection or purification tag, including a FLAG, His6, or Ig sequence; or sequence of another cytokine receptor protein. Kit embodiments include ones comprising a described polypeptide, and: a compartment comprising the protein or polypeptide; or instructions for use or disposal of reagents in the kit.

Binding compositions are provided, e.g., comprising an antigen binding site from an antibody, which specifically binds to a natural DCRS8 or DCRS9 polypeptide, wherein: the binding compound is in a container; the DCRS8 or DCRS9 polypeptide is from a human; the binding compound is an Fv, Fab, or Fab2 fragment; the binding compound is conjugated to another chemical moiety; or the antibody: is raised against a peptide sequence of a mature polypeptide of Table 3 or 4; is raised against a mature DCRS8 or DCRS9; is raised to a purified human DCRS8 or DCRS9; is immunoselected; is a polyclonal antibody; binds to a denatured DCRS8 or DCRS9; exhibits a Kd to antigen of at least 30 μM; is attached to a solid substrate, including a bead or plastic membrane; is in a sterile composition; or is detectably labeled, including a radioactive or fluorescent label. Kits include ones comprising such a binding compound, and: a compartment

comprising the binding compound; or instructions for use or disposal of reagents in the kit.

The invention also provides methods of producing an antigen:antibody complex, comprising contacting under appropriate conditions a primate DCRS8 or DCRS9 polypeptide with a described antibody, thereby allowing the complex to form. Preferred methods include ones wherein: the complex is purified from other cytokine receptors; the complex is purified from other antibody; the contacting is with a sample comprising an interferon; the contacting allows quantitative detection of the antigen; the contacting is with a sample comprising the antibody; or the contacting allows quantitative detection of the antibody. Further compositions include those comprising: a sterile binding compound, as described, or the binding compound and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration.

Nucleic acid compositions include an isolated or recombinant nucleic acid encoding a desribed polypeptide wherein the: DCRS8 or DCRS9 is from a human; or the nucleic acid: encodes an antigenic peptide sequence of Table 3 or 4; encodes a plurality of antigenic peptide sequences of Table 3 or 4; exhibits identity over at least thirteen nucleotides to a natural cDNA encoding the segment; is an expression vector; further comprises an origin of replication; is from a natural source; comprises a detectable label; comprises synthetic nucleotide sequence; is less than 6 kb, preferably less than 3 kb; is from a primate; comprises a natural full length coding sequence; is a hybridization probe for a gene encoding the DCRS8 or DCRS9; or is a PCR primer, PCR product, or mutagenesis primer. Also provided are a cell or tissue comprising such a recombinant nucleic acid, e.g., where the cell is: a prokaryotic cell; a eukaryotic cell; a bacterial cell; a yeast cell; an insect cell; a mammalian cell; a mouse cell; a primate cell; or a human cell.

Kit embodiments include those comprising a described nucleic acid and: a compartment comprising the nucleic acid; a compartment further comprising a primate DCRS8 or DCRS9 polypeptide; or instructions for use or disposal of reagents in the kit.

Other nucleic acids provided include ones which: hybridize under wash conditions of 30 minutes at 30° C and less than 2M salt to the coding portion of SEQ ID NO: 13 or 16; or exhibit identity over a stretch of at least about 30 nucleotides to a primate DCRS8 or DCRS9. Preferably, such will be nucleic acids where: the wash conditions are: at 45° C and/or 500 mM salt; at 55° C and/or 150 mM salt; or the stretch is at least 55 or 75 nucleotides.

Also provided are methods of modulating physiology or development of a cell or tissue culture cells comprising contacting the cell with an agonist or antagonist of a

mammalian DCRS8 or DCRS9. Preferably, the cell is transformed with a nucleic acid encoding the DCRS8 or DCRS9 and another cytokine receptor subunit.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

OUTLINE

I. General

The present invention provides the amino acid sequence and DNA sequence of mammalian, herein primate, cytokine receptor-like subunit molecules, these designated DNAX Cytokine Receptor Subunits 6 (DCRS6), 7 (DCRS7), 8 (DCRS8), 9 (DCRS9), and 10 (DCRS10) having particular defined properties, both structural and biological.

Various cDNAs encoding these molecules were obtained from primate, e.g., human, and/or rodent, e.g., mouse, cDNA sequence libraries. Other primate or other mammalian counterparts would also be desired.

Some of the standard methods applicable are described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.), vols. 1-3, CSH Press, NY; Ausubel, et al., Biology, Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and periodic supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York; each of which is incorporated herein by reference.

Nucleotide (SEQ ID NO: 1) and corresponding amino acid sequence (SEQ ID NO: 2) of a primate, e.g., human, DCRS6 coding segment is shown in Table 1 along with reverse translation (SEQ ID NO: 3). Rodent, e.g., mouse, counterpart sequences are provided, e.g., SEQ ID NO: 4-6.

Similarly, nucleotide (SEQ ID NO: 7) and corresponding amino acid sequence (SEQ ID NO: 8) of a primate, e.g., human, DCRS7 coding segment is shown in Table 2 along with reverse translation (SEQ ID NO: 9). Rodent, e.g., mouse, counterpart sequences are provided, e.g., SEQ ID NO: 10-12. Nucleotide (SEQ ID NO: 13) and corresponding amino acid sequence (SEQ ID NO: 14) of a primate, e.g., human, DCRS8 coding segment is shown in Table 3 along with reverse translation (SEQ ID NO: 15).

Nucleotide (SEQ ID NO: 16) and corresponding amino acid sequence (SEQ ID NO: 17) of a primate, e.g., human, DCRS9 coding segment is shown in Table 4 along with reverse translation (SEQ ID NO: 18). Rodent, e.g., mouse, counterpart sequences are provided, e.g., SEQ ID NO: 19-21. Nucleotide (SEQ ID NO: 22) and corresponding amino acid sequence (SEQ ID NO: 23) of a primate, e.g., human, DCRS10 coding segment is shown in Table 5 along with reverse translation (SEQ ID NO: 24). Rodent, e.g., mouse, counterpart sequences are provided, e.g., SEQ ID NO: 26-27.

Table 1: Nucleotide and polypeptide sequences of DNAX Cytokine Receptor Subunit like embodiments (DCRS6). Primate, e.g., human, embodiment (see SEQ ID NO: 1 and 2). Predicted signal sequence indicated, but may vary by a few positions and depending upon cell type.

```
gcg atg tcg ctc gtg ctg cta agc ctg gcc gcg ctg tgc agg agc gcc    48
    Met Ser Leu Val Leu Leu Ser Leu Ala Ala Leu Cys Arg Ser Ala
                    -10                 -5                  -1   1

gta ccc cga gag ccg acc gtt caa tgt ggc tct gaa act ggg cca tct    96
Val Pro Arg Glu Pro Thr Val Gln Cys Gly Ser Glu Thr Gly Pro Ser
            5                   10                  15
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cca gag tgg atg cta caa cat gat cta atc ccg gga gac ttg agg gac     144
Pro Glu Trp Met Leu Gln His Asp Leu Ile Pro Gly Asp Leu Arg Asp
        20                  25                  30

ctc cga gta gaa cct gtt aca act agt gtt gca aca ggg gac tat tca     192
Leu Arg Val Glu Pro Val Thr Thr Ser Val Ala Thr Gly Asp Tyr Ser
    35                  40                  45

att ttg atg aat gta agc tgg gta ctc cgg gca gat gcc agc atc cgc     240
Ile Leu Met Asn Val Ser Trp Val Leu Arg Ala Asp Ala Ser Ile Arg
50                  55                  60                  65

ttg ttg aag gcc acc aag att tgt gtg acg ggc aaa agc aac ttc cag     288
Leu Leu Lys Ala Thr Lys Ile Cys Val Thr Gly Lys Ser Asn Phe Gln
                70                  75                  80

tcc tac agc tgt gtg agg tgc aat tac aca gag gcc ttc cag act cag     336
Ser Tyr Ser Cys Val Arg Cys Asn Tyr Thr Glu Ala Phe Gln Thr Gln
            85                  90                  95

acc aga ccc tct ggt ggt aaa tgg aca ttt tcc tat atc ggc ttc cct     384
Thr Arg Pro Ser Gly Gly Lys Trp Thr Phe Ser Tyr Ile Gly Phe Pro
        100                 105                 110

gta gag ctg aac aca gtc tat ttc att ggg gcc cat aat att cct aat     432
Val Glu Leu Asn Thr Val Tyr Phe Ile Gly Ala His Asn Ile Pro Asn
    115                 120                 125

gca aat atg aat gaa gat ggc cct tcc atg tct gtg aat ttc acc tca     480
Ala Asn Met Asn Glu Asp Gly Pro Ser Met Ser Val Asn Phe Thr Ser
130                 135                 140                 145

cca ggc tgc cta gac cac ata atg aaa tat aaa aaa aag tgt gtc aag     528
Pro Gly Cys Leu Asp His Ile Met Lys Tyr Lys Lys Lys Cys Val Lys
                150                 155                 160

gcc gga agc ctg tgg gat ccg aac atc act gct tgt aag aag aat gag     576
Ala Gly Ser Leu Trp Asp Pro Asn Ile Thr Ala Cys Lys Lys Asn Glu
            165                 170                 175

gag aca gta gaa gtg aac ttc aca acc act ccc ctg gga aac aga tac     624
Glu Thr Val Glu Val Asn Phe Thr Thr Thr Pro Leu Gly Asn Arg Tyr
        180                 185                 190

atg gct ctt atc caa cac agc act atc atc ggg ttt tct cag gtg ttt     672
Met Ala Leu Ile Gln His Ser Thr Ile Ile Gly Phe Ser Gln Val Phe
    195                 200                 205

gag cca cac cag aag aaa caa acg cga gct tca gtg gtg att cca gtg     720
Glu Pro His Gln Lys Lys Gln Thr Arg Ala Ser Val Val Ile Pro Val
210                 215                 220                 225

act ggg gat agt gaa ggt gct acg gtg cag ctg act cca tat ttt cct     768
Thr Gly Asp Ser Glu Gly Ala Thr Val Gln Leu Thr Pro Tyr Phe Pro
                230                 235                 240
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act tgt ggc agc gac tgc atc cga cat aaa gga aca gtt gtg ctc tgc    816
Thr Cys Gly Ser Asp Cys Ile Arg His Lys Gly Thr Val Val Leu Cys
            245                 250                 255

cca caa aca ggc gtc cct ttc cct ctg gat aac aac aaa agc aag ccg    864
Pro Gln Thr Gly Val Pro Phe Pro Leu Asp Asn Asn Lys Ser Lys Pro
        260                 265                 270

gga ggc tgg ctg cct ctc ctc ctg ctg tct ctg ctg gtg gcc aca tgg    912
Gly Gly Trp Leu Pro Leu Leu Leu Leu Ser Leu Leu Val Ala Thr Trp
    275                 280                 285

gtg ctg gtg gca ggg atc tat cta atg tgg agg cac gaa agg atc aag    960
Val Leu Val Ala Gly Ile Tyr Leu Met Trp Arg His Glu Arg Ile Lys
290                 295                 300                 305

aag act tcc ttt tct acc acc aca cta ctg ccc ccc att aag gtt ctt   1008
Lys Thr Ser Phe Ser Thr Thr Thr Leu Leu Pro Pro Ile Lys Val Leu
                310                 315                 320

gtg gtt tac cca tct gaa ata tgt ttc cat cac aca att tgt tac ttc   1056
Val Val Tyr Pro Ser Glu Ile Cys Phe His His Thr Ile Cys Tyr Phe
            325                 330                 335

act gaa ttt ctt caa aac cat tgc aga agt gag gtc atc ctt gaa aag   1104
Thr Glu Phe Leu Gln Asn His Cys Arg Ser Glu Val Ile Leu Glu Lys
        340                 345                 350

tgg cag aaa aag aaa ata gca gag atg ggt cca gtg cag tgg ctt gcc   1152
Trp Gln Lys Lys Lys Ile Ala Glu Met Gly Pro Val Gln Trp Leu Ala
    355                 360                 365

act caa aag aag gca gca gac aaa gtc gtc ttc ctt ctt tcc aat gac   1200
Thr Gln Lys Lys Ala Ala Asp Lys Val Val Phe Leu Leu Ser Asn Asp
370                 375                 380                 385

gtc aac agt gtg tgc gat ggt acc tgt ggc aag agc gag ggc agt ccc   1248
Val Asn Ser Val Cys Asp Gly Thr Cys Gly Lys Ser Glu Gly Ser Pro
                390                 395                 400

agt gag aac tct caa gac ctc ttc ccc ctt gcc ttt aac ctt ttc tgc   1296
Ser Glu Asn Ser Gln Asp Leu Phe Pro Leu Ala Phe Asn Leu Phe Cys
            405                 410                 415

agt gat cta aga agc cag att cat ctg cac aaa tac gtg gtg gtc tac   1344
Ser Asp Leu Arg Ser Gln Ile His Leu His Lys Tyr Val Val Val Tyr
        420                 425                 430

ttt aga gag att gat aca aaa gac gat tac aat gct ctc agt gtc tgc   1392
Phe Arg Glu Ile Asp Thr Lys Asp Asp Tyr Asn Ala Leu Ser Val Cys
    435                 440                 445

ccc aag tac cac ctc atg aag gat gcc act gct ttc tgt gca gaa ctt   1440
Pro Lys Tyr His Leu Met Lys Asp Ala Thr Ala Phe Cys Ala Glu Leu
450                 455                 460                 465
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ctc cat gtc aag cag cag gtg tca gca gga aaa aga tca caa gcc tgc    1488
Leu His Val Lys Gln Gln Val Ser Ala Gly Lys Arg Ser Gln Ala Cys
                470                     475                     480

cac gat ggc tgc tgc tcc ttg tagcccaccc atgagaagca agagacctta       1539
His Asp Gly Cys Cys Ser Leu
            485

aaggcttcct atcccaccaa ttacagggaa aaaacgtgtg atgatcctga agcttactat 1599

gcagcctaca aacagcctta gtaattaaaa cattttatac caataaaatt ttcaaatatt 1659

gctaactaat gtagcattaa ctaacgattg gaaactacat ttacaacttc aaagctgttt 1719

tatacataga aatcaattac agctttaatt gaaaactgta accattttga taatgcaaca 1779

ataaagcatc ttcagcc                                                 1796
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MSLVLLSLAALCRSAVPREPTVQCGSETGPSPEWMLQHDLIPGDLRDLRVEPVTTSVATGDYSILMNVSWVL
RADASIRLLKATKICVTGKSNFQSYSCVRCNYTEAFQTQTRPSGGKWTFSYIGFPVELNTVYFIGAHNIPNA
NMNEDGPSMSVNFTSPGCLDHIMKYKKKCVKAGSLWDPNITACKKNEETVEVNFTTTPLGNRYMALIQHSTI
IGFSQVFEPHQKKQTRASVVIPVTGDSEGATVQLTPYFPTCGSDCIRHKGTVVLCPQTGVPFPLDNNKSKPG
GWLPLLLLSLLVATWVLVAGIYLMWRHERIKKTSFSTTTLLPPIKVLVVYPSEICFHHTICYFTEFLQNHCR
SEVILEKWQKKKIAEMGPVQWLATQKKAADKVVFLLSNDVNSVCDGTCGKSEGSPSENSQDLFPLAFNLFCS
DLRSQIHLHKYVVVYFREIDTKDDYNALSVCPKYHLMKDATAFCAELLHVKQQVSAGKRSQACHDGCCSL.

Reverse translation of primate, e.g., human, DCRS6 (SEQ ID NO: 3):

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atgwsnytng tnytnytnws nytngcngcn ytntgymgnw sngcngtncc nmgngarccn 60

acngtncart gyggnwsnga racnggnccn wsnccngart ggatgytnca rcaygayytn 120

athccnggng ayytnmgnga yytnmgngtn garccngtna cnacnwsngt ngcnacnggn 180

gaytaywsna thytnatgaa ygtnwsntgg gtnytnmgng cngaygcnws nathmgnytn 240

ytnaargcna cnaarathtg ygtnacnggn aarwsnaayt tycarwsnta ywsntgygtn 300

mgntgyaayt ayacngargc nttycaracn caracnmgnc cnwsnggngg naartggacn 360

ttywsntaya thggnttycc ngtngarytn aayacngtnt ayttyathgg ngcncayaay 420

athccnaayg cnaayatgaa ygargayggn ccnwsnatgw sngtnaaytt yacnwsnccn 480

ggntgyytng aycayathat gaartayaar aaraartgyg tnaargcngg nwsnytntgg 540

gayccnaaya thacngcntg yaaraaraay gargaracng tngargtnaa yttyacnacn 600

acnccnytng gnaaymgnta yatggcnytn athcarcayw snacnathat hggnttywsn 660

cargtnttyg arccncayca raaraarcar acnmgngcnw sngtngtnat hccngtnacn 720

ggngaywsng arggngcnac ngtncarytn acnccntayt tyccnacntg yggnwsngay 780

tgyathmgnc ayaarggnac ngtngtnytn tgyccncara cnggngtncc nttyccnytn 840

gayaayaaya arwsnaarcc nggnggntgg ytnccnytny tnytnytnws nytnytngtn 900
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gcnacntggg tnytngtngc nggnathtay ytnatgtggm gncaygarmg nathaaraar 960
acnwsnttyw snacnacnac nytnytnccn ccnathaarg tnytngtngt ntayccnwsn 1020
garathtgyt tycaycayac nathtgytay ttyacngart tyytncaraa ycaytgymgn 1080
wsngargtna thytngaraa rtggcaraar aaraarathg cngaratggg nccngtncar 1140
tggytngcna cncaraaraa rgcngcngay aargtngtnt tyytnytnws naaygaygtn 1200
aaywsngtnt gygayggnac ntgyggnaar wsngarggnw snccnwsnga raaywsncar 1260
gayytnttyc cnytngcntt yaayytntty tgywsngayy tnmgnwsnca rathcayytn 1320
cayaartayg tngtngtnta yttymgngar athgayacna argaygayta yaaygcnytn 1380
wsngtntgyc cnaartayca yytnatgaar gaygcnacng cnttytgygc ngarytnytn 1440
caygtnaarc arcargtnws ngcnggnaar mgnwsncarg cntgycayga yggntgytgy 1500
wsnytn                                                            1506
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Rodent, e.g., mouse embodiment (see SEQ ID NO: 4 and 5).

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gat ttc agc agc cag acg cat ctg cac aaa tac ctg gag gtc tat ctt    48
Asp Phe Ser Ser Gln Thr His Leu His Lys Tyr Leu Glu Val Tyr Leu
  1               5                  10                  15

ggg gga gca gac ctc aaa ggc gac tat aat gcc ctg agt gtc tgc ccc    96
Gly Gly Ala Asp Leu Lys Gly Asp Tyr Asn Ala Leu Ser Val Cys Pro
             20                  25                  30

caa tat cat ctc atg aag gac gcc aca gct ttc cac aca gaa ctt ctc   144
Gln Tyr His Leu Met Lys Asp Ala Thr Ala Phe His Thr Glu Leu Leu
         35                  40                  45

aag gct acg cag agc atg tca gtg aag aaa cgc tca caa gcc tgc cat   192
Lys Ala Thr Gln Ser Met Ser Val Lys Lys Arg Ser Gln Ala Cys His
     50                  55                  60

gat agc tgt tca ccc ttg tagtccaccc gggggaatag agactctgaa          240
Asp Ser Cys Ser Pro Leu
 65                  70

gccttcctac tctcccttcc agtgacaaat gctgtgtgac gactctgaaa tgtgtgggag 300
aggctgtgtg gaggtagtgc tatgtacaaa cttgctttaa aactggagtt tgcaaagtca 360
acctgagcat acacgcctga ggctagtcat tggctggatt tatgaagaca acacagttac 420
agacaataat gagtgggacc tacatttggg atatacccaa agctgggtaa tgattatcac 480
tgagaaccac gcactctggc catgaggtaa tacggcactt ccctgtcagg ctgtctgtca 540
ggttgggtct gtcttgcact gcccatgctc tatgctgcac gtagaccgtt ttgtaacatt 600
ttaatctgtt aatgaataat ccgtttggga ggctctc                          637
```

DFSSQTHLHKYLEVYLGGADLKGDYNALSVCPQYHLMKDATAFHTELLKATQSMSVKKRSQACHDSCSPL.

Reverse translation of rodent, e.g., mouse, DCRS6 (SEQ ID NO: 6):

```
gayttywsnw sncaracnca yytncayaar tayytngarg tntayytngg nggngcngay 60
ytnaarggng aytayaaygc nytnwsngtn tgyccncart aycayytnat gaargaygcn 120
acngcnttyc ayacngaryt nytnaargcn acncarwsna tgwsngtnaa raarmgnwsn 180
cargcntgyc aygaywsntg ywsnccnytn                                  210
```

Table 2: Nucleotide and polypeptide sequences of DNAX Cytokine Receptor Subunit like embodiments (DCRS7). Primate, e.g., human, embodiment (see SEQ ID NO: 7 and 8). Predicted signal sequence indicated, but may vary by a few positions and depending upon cell type.

```
gagtcaggac tcccaggaca gagagtgcac aaactaccca gcacagcccc ctccgccccc 60
tctggaggct gaagagggat tccagcccct gccacccaca gacacgggct gactggggtg 120
tctgcccccc ttgggggcan ccacagggcc tcaggcctgg gtgccacctg gcactagaag 180

atg cct gtg ccc tgg ttc ttg ctg tcc ttg gca ctg ggc cga agc cag   228
Met Pro Val Pro Trp Phe Leu Leu Ser Leu Ala Leu Gly Arg Ser Gln
-20                 -15                 -10                 -5

tgg atc ctt tct ctg gag agg ctt gtg ggg cct cag gac gct acc cac   276
Trp Ile Leu Ser Leu Glu Arg Leu Val Gly Pro Gln Asp Ala Thr His
            -1   1                  5                  10

tgc tct ccg ggc ctc tcc tgc cgc ctc tgg gac agt gac ata ctc tgc   324
Cys Ser Pro Gly Leu Ser Cys Arg Leu Trp Asp Ser Asp Ile Leu Cys
        15                  20                  25

ctg cct ggg gac atc gtg cct gct ccg ggc ccc gtg ctg gcg cct acg   372
Leu Pro Gly Asp Ile Val Pro Ala Pro Gly Pro Val Leu Ala Pro Thr
    30                  35                  40

cac ctg cag aca gag ctg gtg ctg agg tgc cag aag gag acc gac tgt   420
His Leu Gln Thr Glu Leu Val Leu Arg Cys Gln Lys Glu Thr Asp Cys
45                  50                  55                  60

gac ctc tgt ctg cgt gtg gct gtc cac ttg gcc gtg cat ggg cac tgg   468
Asp Leu Cys Leu Arg Val Ala Val His Leu Ala Val His Gly His Trp
                65                  70                  75

gaa gag cct gaa gat gag gaa aag ttt gga gga gca gct gac tta ggg   516
Glu Glu Pro Glu Asp Glu Glu Lys Phe Gly Gly Ala Ala Asp Leu Gly
            80                  85                  90

gtg gag gag cct agg aat gcc tct ctc cag gcc caa gtc gtg ctc tcc   564
Val Glu Glu Pro Arg Asn Ala Ser Leu Gln Ala Gln Val Val Leu Ser
        95                  100                 105
```

```
ttc cag gcc tac cct act gcc cgc tgc gtc ctg ctg gag gtg caa gtg    612
Phe Gln Ala Tyr Pro Thr Ala Arg Cys Val Leu Leu Glu Val Gln Val
    110                 115                 120

cct gct gcc ctt gtg cag ttt ggt cag tct gtg ggc tct gtg gta tat    660
Pro Ala Ala Leu Val Gln Phe Gly Gln Ser Val Gly Ser Val Val Tyr
125                 130                 135                 140

gac tgc ttc gag gct gcc cta ggg agt gag gta cga atc tgg tcc tat    708
Asp Cys Phe Glu Ala Ala Leu Gly Ser Glu Val Arg Ile Trp Ser Tyr
                145                 150                 155

act cag ccc agg tac gag aag gaa ctc aac cac aca cag cag ctg cct    756
Thr Gln Pro Arg Tyr Glu Lys Glu Leu Asn His Thr Gln Gln Leu Pro
            160                 165                 170

gac tgc agg ggg ctc gaa gtc tgg aac agc atc ccg agc tgc tgg gcc    804
Asp Cys Arg Gly Leu Glu Val Trp Asn Ser Ile Pro Ser Cys Trp Ala
        175                 180                 185

ctg ccc tgg ctc aac gtg tca gca gat ggt gac aac gtg cat ctg gtt    852
Leu Pro Trp Leu Asn Val Ser Ala Asp Gly Asp Asn Val His Leu Val
    190                 195                 200

ctg aat gtc tct gag gag cag cac ttc ggc ctc tcc ctg tac tgg aat    900
Leu Asn Val Ser Glu Glu Gln His Phe Gly Leu Ser Leu Tyr Trp Asn
205                 210                 215                 220

cag gtc cag ggc ccc cca aaa ccc cgg tgg cac aaa aac ctg act gga    948
Gln Val Gln Gly Pro Pro Lys Pro Arg Trp His Lys Asn Leu Thr Gly
                225                 230                 235

ccg cag atc att acc ttg aac cac aca gac ctg gtt ccc tgc ctc tgt    996
Pro Gln Ile Ile Thr Leu Asn His Thr Asp Leu Val Pro Cys Leu Cys
            240                 245                 250

att cag gtg tgg cct ctg gaa cct gac tcc gtt agg acg aac atc tgc    1044
Ile Gln Val Trp Pro Leu Glu Pro Asp Ser Val Arg Thr Asn Ile Cys
        255                 260                 265

ccc ttc agg gag gac ccc cgc gca cac cag aac ctc tgg caa gcc gcc    1092
Pro Phe Arg Glu Asp Pro Arg Ala His Gln Asn Leu Trp Gln Ala Ala
    270                 275                 280

cga ctg cga ctg ctg acc ctg cag agc tgg ctg ctg gac gca ccg tgc    1140
Arg Leu Arg Leu Leu Thr Leu Gln Ser Trp Leu Leu Asp Ala Pro Cys
285                 290                 295                 300

tcg ctg ccc gca gaa gcg gca ctg tgc tgg cgg gct ccg ggt ggg gac    1188
Ser Leu Pro Ala Glu Ala Ala Leu Cys Trp Arg Ala Pro Gly Gly Asp
                305                 310                 315

ccc tgc cag cca ctg gtc cca ccg ctt tcc tgg gag aat gtc act gtg    1236
Pro Cys Gln Pro Leu Val Pro Pro Leu Ser Trp Glu Asn Val Thr Val
            320                 325                 330

gac gtg aac agc tcg gag aag ctg cag ctg cag gag tgc ttg tgg gct    1284
Asp Val Asn Ser Ser Glu Lys Leu Gln Leu Gln Glu Cys Leu Trp Ala
        335                 340                 345
```

```
gac tcc ctg ggg cct ctc aaa gac gat gtg cta ctg ttg gag aca cga    1332
Asp Ser Leu Gly Pro Leu Lys Asp Asp Val Leu Leu Leu Glu Thr Arg
    350                 355                 360

ggc ccc cag gac aac aga tcc ctc tgt gcc ttg gaa ccc agt ggc tgt    1380
Gly Pro Gln Asp Asn Arg Ser Leu Cys Ala Leu Glu Pro Ser Gly Cys
365                 370                 375                 380

act tca cta ccc agc aaa gcc tcc acg agg gca gct cgc ctt gga gag    1428
Thr Ser Leu Pro Ser Lys Ala Ser Thr Arg Ala Ala Arg Leu Gly Glu
                385                 390                 395

tac tta cta caa gac ctg cag tca ggc cag tgt ctg cag cta tgg gac    1476
Tyr Leu Leu Gln Asp Leu Gln Ser Gly Gln Cys Leu Gln Leu Trp Asp
            400                 405                 410

gat gac ttg gga gcg cta tgg gcc tgc ccc atg gac aaa tac atc cac    1524
Asp Asp Leu Gly Ala Leu Trp Ala Cys Pro Met Asp Lys Tyr Ile His
        415                 420                 425

aag cgc tgg gcc ctc gtg tgg ctg gcc tgc cta ctc ttt gcc gct gcg    1572
Lys Arg Trp Ala Leu Val Trp Leu Ala Cys Leu Leu Phe Ala Ala Ala
    430                 435                 440

ctt tcc ctc atc ctc ctt ctc aaa aag gat cac gcg aaa ggg tgg ctg    1620
Leu Ser Leu Ile Leu Leu Leu Lys Lys Asp His Ala Lys Gly Trp Leu
445                 450                 455                 460

agg ctc ttg aaa cag gac gtc cgc tcg ggg gcg gcc gcc agg ggc cgc    1668
Arg Leu Leu Lys Gln Asp Val Arg Ser Gly Ala Ala Ala Arg Gly Arg
                465                 470                 475

gcg gct ctg ctc ctc tac tca gcc gat gac tcg ggt ttc gag cgc ctg    1716
Ala Ala Leu Leu Leu Tyr Ser Ala Asp Asp Ser Gly Phe Glu Arg Leu
            480                 485                 490

gtg ggc gcc ctg gcg tcg gcc ctg tgc cag ctg ccg ctg cgc gtg gcc    1764
Val Gly Ala Leu Ala Ser Ala Leu Cys Gln Leu Pro Leu Arg Val Ala
        495                 500                 505

gta gac ctg tgg agc cgt cgt gaa ctg agc gcg cag ggg ccc gtg gct    1812
Val Asp Leu Trp Ser Arg Arg Glu Leu Ser Ala Gln Gly Pro Val Ala
    510                 515                 520

tgg ttt cac gcg cag cgg cgc cag acc ctg cag gag ggc ggc gtg gtg    1860
Trp Phe His Ala Gln Arg Arg Gln Thr Leu Gln Glu Gly Gly Val Val
525                 530                 535                 540

gtc ttg ctc ttc tct ccc ggt gcg gtg gcg ctg tgc agc gag tgg cta    1908
Val Leu Leu Phe Ser Pro Gly Ala Val Ala Leu Cys Ser Glu Trp Leu
                545                 550                 555

cag gat ggg gtg tcc ggg ccc ggg gcg cac ggc ccg cac gac gcc ttc    1956
Gln Asp Gly Val Ser Gly Pro Gly Ala His Gly Pro His Asp Ala Phe
            560                 565                 570
```

```
cgc gcc tcg ctc agc tgc gtg ctg ccc gac ttc ttg cag ggc cgg gcg    2004
Arg Ala Ser Leu Ser Cys Val Leu Pro Asp Phe Leu Gln Gly Arg Ala
        575                 580                 585

ccc ggc agc tac gtg ggg gcc tgc ttc gac agg ctg ctc cac ccg gac    2052
Pro Gly Ser Tyr Val Gly Ala Cys Phe Asp Arg Leu Leu His Pro Asp
    590                 595                 600

gcc gta ccc gcc ctt ttc cgc acc gtg ccc gtc ttc aca ctg ccc tcc    2100
Ala Val Pro Ala Leu Phe Arg Thr Val Pro Val Phe Thr Leu Pro Ser
605                 610                 615                 620

caa ctg cca gac ttc ctg ggg gcc ctg cag cag cct cgc gcc ccg cgt    2148
Gln Leu Pro Asp Phe Leu Gly Ala Leu Gln Gln Pro Arg Ala Pro Arg
            625                 630                 635

tcc ggg cgg ctc caa gag aga gcg gag caa gtg tcc cgg gcc ctt cag    2196
Ser Gly Arg Leu Gln Glu Arg Ala Glu Gln Val Ser Arg Ala Leu Gln
        640                 645                 650

cca gcc ctg gat agc tac ttc cat ccc ccg ggg acn tcc gcg ccg gga    2244
Pro Ala Leu Asp Ser Tyr Phe His Pro Pro Gly Xaa Ser Ala Pro Gly
        655                 660                 665

cgc ggg gtg gga cca ggg gcg gga cct ggg gcg ggg gac ggg act        2289
Arg Gly Val Gly Pro Gly Ala Gly Pro Gly Ala Gly Asp Gly Thr
    670                 675                 680

taaataaagg cagacgctg                                               2308
```

MPVPWFLLSLALGRSQWILSLERLVGPQDATHCSPGLSCRLWDSDILCLPGDIVPAPGPVLAPTHLQTELVL
RCQKETDCDLCLRVAVHLAVHGHWEEPEDEEKFGGAADLGVEEPRNASLQAQVVLSFQAYPTARCVLLEVQV
PAALVQFGQSVGSVVYDCFEAALGSEVRIWSYTQPRYEKELNHTQQLPDCRGLEVWNSIPSCWALPWLNVSA
DGDNVHLVLNVSEEQHFGLSLYWNQVQGPPKPRWHKNLTGPQIITLNHTDLVPCLCIQVWPLEPDSVRTNIC
PFREDPRAHQNLWQAARLRLLTLQSWLLDAPCSLPAEAALCWRAPGGDPCQPLVPPLSWENVTVDVNSSEKL
QLQECLWADSLGPLKDDVLLLETRGPQDNRSLCALEPSGCTSLPSKASTRAARLGEYLLQDLQSGQCLQLWD
DDLGALWACPMDKYIHKRWALVWLACLLFAAALSLILLLKKDHAKGWLRLLKQDVRSGAAARGRAALLLYSA
DDSGFERLVGALASALCQLPLRVAVDLWSRRELSAQGPVAWFHAQRRQTLQEGGVVVLLFSPGAVALCSEWL
QDGVSGPGAHGPHDAFRASLSCVLPDFLQGRAPGSYVGACFDRLLHPDAVPALFRTVPVFTLPSQLPDFLGA
LQQPRAPRSGRLQERAEQVSRALQPALDSYFHPPGTSAPGRGVGPGAGPGAGDGT.

Reverse translation of primate, e.g., human, DCRS7 (SEQ ID NO: 9):

```
atgccngtnc cntggttyyt nytnwsnytn gcnytnggnm gnwsncartg gathytnwsn 60
ytngarmgny tngtnggncc ncargaygcn acncaytgyw snccnggnyt nwsntgymgn 120
ytntgggayw sngayathyt ntgyytnccn ggngayathg tnccngcncc nggnccngtn 180
ytngcnccna cncayytnca racngarytn gtnytnmgnt gycaraarga racngaytgy 240
gayytntgyy tnmgngtngc ngtncayytn gcngtncayg gncaytggga rgarccngar 300
gaygargara arttyggngg ngcngcngay ytnggngtng argarccnmg naaygcnwsn 360
ytncargcnc argtngtnyt nwsnttycar gcntayccna cngcnmgntg ygtnytnytn 420
gargtncarg tnccngcngc nytngtncar ttyggncarw sngtnggnws ngtngtntay 480
```

gaytgyttyg argcngcnyt nggnwsngar gtnmgnatht ggwsntayac ncarccnmgn 540
taygaraarg arytnaayca yacncarcar ytnccngayt gymgnggnyt ngargtntgg 600
aaywsnathc cnwsntgytg ggcnytnccn tggytnaayg tnwsngcnga yggngayaay 660
gtncayytng tnytnaaygt nwsngargar carcayttyg gnytnwsnyt ntaytggaay 720
cargtncarg gnccnccnaa rccnmgntgg cayaaraayy tnacnggncc ncarathath 780
acnytnaayc ayacngayyt ngtnccntgy ytntgyathc argtntggcc nytngarccn 840
gaywsngtnm gnacnaayat htgyccntty mgngargayc cnmgngcnca ycaraayytn 900
tggcargcng cnmgnytnmg nytnytnacn ytncarwsnt ggytnytnga ygcnccntgy 960
wsnytnccng cngargcngc nytntgytgg mgngcnccng gnggngaycc ntgycarccn 1020
ytngtnccnc cnytnwsntg ggaraaygtn acngtngayg tnaaywsnws ngaraarytn 1080
carytncarg artgyytntg ggcngaywsn ytnggnccny tnaargayga ygtnytnytn 1140
ytngaracnm gnggnccnca rgayaaymgn wsnytntgyg cnytngarcc nwsnggntgy 1200
acnwsnytnc cnwsnaargc nwsnacnmgn gcngcnmgny tnggngarta yytnytncar 1260
gayytncarw snggncartg yytncarytn tgggaygayg ayytnggngc nytntgggcn 1320
tgyccnatgg ayaartayat hcayaarmgn tgggcnytng tntggytngc ntgyytnytn 1380
ttygcngcng cnytnwsnyt nathytnytn ytnaaraarg aycaygcnaa rggntggytn 1440
mgnytnytna arcargaygt nmgnwsnggn gcngcngcnm gnggnmgngc ngcnytnytn 1500
ytntaywsng cngaygayws nggnttygar mgnytngtng gngcnytngc nwsngcnytn 1560
tgycarytnc cnytnmgngt ngcngtngay ytntggwsnm gnmgngaryt nwsngcncar 1620
ggnccngtng cntggttyca ygcncarmgn mgncaracny tncargargg nggngtngtn 1680
gtnytnytnt tywsnccngg ngcngtngcn ytntgywsng artggytnca rgayggngtn 1740
wsnggnccng gngcncaygg nccncaygay gcnttymgng cnwsnytnws ntgygtnytn 1800
ccngayttyy tncarggnmg ngcnccnggn wsntaygtng gngcntgytt ygaymgnytn 1860
ytncayccng aygcngtncc ngcnytntty mgnacngtnc cngtnttyac nytnccnwsn 1920
carytnccng ayttyytngg ngcnytncar carccnmgng cnccnmgnws nggnmgnytn 1980
cargarmgng cngarcargt nwsnmgngcn ytncarccng cnytngayws ntayttycay 2040
ccnccnggna cnwsngcncc nggnmgnggn gtnggnccng gngcnggncc nggngcnggn 2100
gayggnacn 2109

Rodent, e.g., mouse, embodiment (see SEQ ID NO: 10 and 11). Predicted signal sequence indicated, but may vary by a few positions and depending upon cell type.

```
ccaaatcgaa agcacgggag ctgatactgg gcctggagtc caggctcact ggagtgggga 60

agcatggctg gagaggaatt ctagcccttg ctctctccca gggacacggg gctgattgtc 120

agcaggggcg aggggtctgc ccccccttgg gggggcagga cggggcctca ggcctgggtg 180

ctgtccggca cctggaag atg cct gtg tcc tgg ttc ctg ctg tcc ttg gca   231
                    Met Pro Val Ser Trp Phe Leu Leu Ser Leu Ala
                    -20                 -15                 -10

ctg ggc cga aac cct gtg gtc gtc tct ctg gag aga ctg atg gag cct   279
Leu Gly Arg Asn Pro Val Val Val Ser Leu Glu Arg Leu Met Glu Pro
                 -5                  -1   1               5

cag gac act gca cgc tgc tct cta ggc ctc tcc tgc cac ctc tgg gat   327
Gln Asp Thr Ala Arg Cys Ser Leu Gly Leu Ser Cys His Leu Trp Asp
        10                  15                  20

ggt gac gtg ctc tgc ctg cct gga agc ctc cag tct gcc cca ggc cct   375
Gly Asp Val Leu Cys Leu Pro Gly Ser Leu Gln Ser Ala Pro Gly Pro
    25                  30                  35

gtg cta gtg cct acc cgc ctg cag acg gag ctg gtg ctg agg tgt cca   423
Val Leu Val Pro Thr Arg Leu Gln Thr Glu Leu Val Leu Arg Cys Pro
 40                  45                  50                  55

cag aag aca gat tgc gcc ctc tgt gtc cgt gtg gtg gtc cac ttg gcc   471
Gln Lys Thr Asp Cys Ala Leu Cys Val Arg Val Val Val His Leu Ala
                 60                  65                  70

gtg cat ggg cac tgg gca gag cct gaa gaa gct gga aag tct gat tca   519
Val His Gly His Trp Ala Glu Pro Glu Glu Ala Gly Lys Ser Asp Ser
            75                  80                  85

gaa ctc cag gag tct agg aac gcc tct ctc cag gcc cag gtg gtg ctc   567
Glu Leu Gln Glu Ser Arg Asn Ala Ser Leu Gln Ala Gln Val Val Leu
        90                  95                 100

tcc ttc cag gcc tac ccc atc gcc cgc tgt gcc ctg ctg gag gtc cag   615
Ser Phe Gln Ala Tyr Pro Ile Ala Arg Cys Ala Leu Leu Glu Val Gln
    105                 110                 115

gtg ccc gct gac ctg gtg cag cct ggt cag tcc gtg ggt tct gcg gta   663
Val Pro Ala Asp Leu Val Gln Pro Gly Gln Ser Val Gly Ser Ala Val
120                 125                 130                 135

ttt gac tgt ttc gag gct agt ctt ggg gct gag gta cag atc tgg tcc   711
Phe Asp Cys Phe Glu Ala Ser Leu Gly Ala Glu Val Gln Ile Trp Ser
                140                 145                 150

tac acg aag ccc agg tac cag aaa gag ctc aac ctc aca cag cag ctg   759
Tyr Thr Lys Pro Arg Tyr Gln Lys Glu Leu Asn Leu Thr Gln Gln Leu
            155                 160                 165
```

```
cct gac tgc agg ggt ctt gaa gtc cgg gac agc atc cag agc tgc tgg    807
Pro Asp Cys Arg Gly Leu Glu Val Arg Asp Ser Ile Gln Ser Cys Trp
        170                 175                 180

gtc ctg ccc tgg ctc aat gtg tct aca gat ggt gac aat gtc ctt ctg    855
Val Leu Pro Trp Leu Asn Val Ser Thr Asp Gly Asp Asn Val Leu Leu
    185                 190                 195

aca ctg gat gtc tct gag gag cag gac ttt agc ttc tta ctg tac ctg    903
Thr Leu Asp Val Ser Glu Glu Gln Asp Phe Ser Phe Leu Leu Tyr Leu
200                 205                 210                 215

cgt cca gtc ccg gat gct ctc aaa tcc ttg tgg tac aaa aac ctg act    951
Arg Pro Val Pro Asp Ala Leu Lys Ser Leu Trp Tyr Lys Asn Leu Thr
                220                 225                 230

gga cct cag aac att act tta aac cac aca gac ctg gtt ccc tgc ctc    999
Gly Pro Gln Asn Ile Thr Leu Asn His Thr Asp Leu Val Pro Cys Leu
            235                 240                 245

tgc att cag gtg tgg tcg cta gag cca gac tct gag agg gtc gaa ttc    1047
Cys Ile Gln Val Trp Ser Leu Glu Pro Asp Ser Glu Arg Val Glu Phe
        250                 255                 260

tgc ccc ttc cgg gaa gat ccc ggt gca cac agg aac ctc tgg cac ata    1095
Cys Pro Phe Arg Glu Asp Pro Gly Ala His Arg Asn Leu Trp His Ile
    265                 270                 275

gcc agg ctg cgg gta ctg tcc cca ggg gta tgg cag cta gat gcg cct    1143
Ala Arg Leu Arg Val Leu Ser Pro Gly Val Trp Gln Leu Asp Ala Pro
280                 285                 290                 295

tgc tgt ctg ccg ggc aag gta aca ctg tgc tgg cag gca cca gac cag    1191
Cys Cys Leu Pro Gly Lys Val Thr Leu Cys Trp Gln Ala Pro Asp Gln
                300                 305                 310

agt ccc tgc cag cca ctt gtg cca cca gtg ccc cag aag aac gcc act    1239
Ser Pro Cys Gln Pro Leu Val Pro Pro Val Pro Gln Lys Asn Ala Thr
            315                 320                 325

gtg aat gag cca caa gat ttc cag ttg gtg gca ggc cac ccc aac ctc    1287
Val Asn Glu Pro Gln Asp Phe Gln Leu Val Ala Gly His Pro Asn Leu
        330                 335                 340

tgt gtc cag gtg agc acc tgg gag aag gtt cag ctg caa gcg tgc ttg    1335
Cys Val Gln Val Ser Thr Trp Glu Lys Val Gln Leu Gln Ala Cys Leu
    345                 350                 355

tgg gct gac tcc ttg ggg ccc ttc aag gat gat atg ctg tta gtg gag    1383
Trp Ala Asp Ser Leu Gly Pro Phe Lys Asp Asp Met Leu Leu Val Glu
360                 365                 370                 375

atg aaa acc ggc ctc aac aac aca tca gtc tgt gcc ttg gaa ccc agt    1431
Met Lys Thr Gly Leu Asn Asn Thr Ser Val Cys Ala Leu Glu Pro Ser
                380                 385                 390

ggc tgt aca cca ctg ccc agc atg gcc tcc acg aga gct gct cgc ctg    1479
Gly Cys Thr Pro Leu Pro Ser Met Ala Ser Thr Arg Ala Ala Arg Leu
            395                 400                 405
```

```
gga gag gag ttg ctg caa gac ttc cga tca cac cag tgt atg cag ctg    1527
Gly Glu Glu Leu Leu Gln Asp Phe Arg Ser His Gln Cys Met Gln Leu
        410                 415                 420

tgg aac gat gac aac atg gga tcg cta tgg gcc tgc ccc atg gac aag    1575
Trp Asn Asp Asp Asn Met Gly Ser Leu Trp Ala Cys Pro Met Asp Lys
    425                 430                 435

tac atc cac agg cgc tgg gtc cta gta tgg ctg gcc tgc cta ctc ttg    1623
Tyr Ile His Arg Arg Trp Val Leu Val Trp Leu Ala Cys Leu Leu Leu
440                 445                 450                 455

gct gcg gcg ctt ttc ttc ttc ctc ctt cta aaa aag gac cgc agg aaa    1671
Ala Ala Ala Leu Phe Phe Phe Leu Leu Leu Lys Lys Asp Arg Arg Lys
            460                 465                 470

gcg gcc cgt ggc tcc cgc acg gcc ttg ctc ctc cac tcc gcc gac gga    1719
Ala Ala Arg Gly Ser Arg Thr Ala Leu Leu Leu His Ser Ala Asp Gly
        475                 480                 485

gcg ggc tac gag cgc ctg gtg gga gca ctg gcg tcc gcg ttg agc cag    1767
Ala Gly Tyr Glu Arg Leu Val Gly Ala Leu Ala Ser Ala Leu Ser Gln
        490                 495                 500

atg cca ctg cgc gtg gcc gtg gac ctg tgg agc cgc cgc gag ctg agc    1815
Met Pro Leu Arg Val Ala Val Asp Leu Trp Ser Arg Arg Glu Leu Ser
    505                 510                 515

gcg cac gga gcc cta gcc tgg ttc cac cac cag cga cgc cgt atc ctg    1863
Ala His Gly Ala Leu Ala Trp Phe His His Gln Arg Arg Arg Ile Leu
520                 525                 530                 535

cag gag ggt ggc gtg gta atc ctt ctc ttc tcg ccc gcg gcc gtg gcg    1911
Gln Glu Gly Gly Val Val Ile Leu Leu Phe Ser Pro Ala Ala Val Ala
            540                 545                 550

cag tgt cag cag tgg ctg cag ctc cag aca gtg gag ccc ggg ccg cat    1959
Gln Cys Gln Gln Trp Leu Gln Leu Gln Thr Val Glu Pro Gly Pro His
        555                 560                 565

gac gcc ctc gcc gcc tgg ctc agc tgc gtg cta ccc gat ttc ctg caa    2007
Asp Ala Leu Ala Ala Trp Leu Ser Cys Val Leu Pro Asp Phe Leu Gln
        570                 575                 580

ggc cgg gcg acc ggc cgc tac gtc ggg gtc tac ttc gac ggg ctg ctg    2055
Gly Arg Ala Thr Gly Arg Tyr Val Gly Val Tyr Phe Asp Gly Leu Leu
    585                 590                 595

cac cca gac tct gtg ccc tcc ccg ttc cgc gtc gcc ccg ctc ttc tcc    2103
His Pro Asp Ser Val Pro Ser Pro Phe Arg Val Ala Pro Leu Phe Ser
600                 605                 610                 615

ctg ccc tcg cag ctg ccg gct ttc ctg gat gca ctg cag gga ggc tgc    2151
Leu Pro Ser Gln Leu Pro Ala Phe Leu Asp Ala Leu Gln Gly Gly Cys
            620                 625                 630
```

```
tcc act tcc gcg ggg cga ccc gcg gac cgg gtg gaa cga gtg acc cag   2199
Ser Thr Ser Ala Gly Arg Pro Ala Asp Arg Val Glu Arg Val Thr Gln
            635                 640                 645

gcg ctg cgg tcc gcc ctg gac agc tgt act tct agc tcg gaa gcc cca   2247
Ala Leu Arg Ser Ala Leu Asp Ser Cys Thr Ser Ser Ser Glu Ala Pro
        650                 655                 660

ggc tgc tgc gag gaa tgg gac ctg gga ccc tgc act aca cta gaa       2292
Gly Cys Cys Glu Glu Trp Asp Leu Gly Pro Cys Thr Thr Leu Glu
    665                 670                 675

taaaagccga tacagtattc ct                                          2314
```

```
MPVSWFLLSLALGRNPVVVSLERLMEPQDTARCSLGLSCHLWDGDVLCLPGSLQSAPGPVLVPTRLQTELVL
RCPQKTDCALCVRVVVHLAVHGHWAEPEEAGKSDSELQESRNASLQAQVVLSFQAYPIARCALLEVQVPADL
VQPGQSVGSAVFDCFEASLGAEVQIWSYTKPRYQKELNLTQQLPDCRGLEVRDSIQSCWVLPWLNVSTDGDN
VLLTLDVSEEQDFSFLLYLRPVPDALKSLWYKNLTGPQNITLNHTDLVPCLCIQVWSLEPDSERVEFCPFRE
DPGAHRNLWHIARLRVLSPGVWQLDAPCCLPGKVTLCWQAPDQSPCQPLVPPVPQKNATVNEPQDFQLVAGH
PNLCVQVSTWEKVQLQACLWADSLGPFKDDMLLVEMKTGLNNTSVCALEPSGCTPLPSMASTRAARLGEELL
QDFRSHQCMQLWNDDNMGSLWACPMDKYIHRRWVLVWLACLLLAAALFFFLLLKKDRRKAARGSRTALLLHS
ADGAGYERLVGALASALSQMPLRVAVDLWSRRELSAHGALAWFHHQRRRILQEGGVVILLFSPAAVAQCQQW
LQLQTVEPGPHDALAAWLSCVLPDFLQGRATGRYVGVYFDGLLHPDSVPSPFRVAPLFSLPSQLPAFLDALQ
GGCSTSAGRPADRVERVTQALRSALDSCTSSSEAPGCCEEWDLGPCTTLE.
```

Reverse translation of rodent, e.g., mouse, DCRS7 (SEQ ID NO: 12):

```
atgccngtnw sntggttyyt nytnwsnytn gcnytnggnm gnaayccngt ngtngtnwsn 60
ytngarmgny tnatggarcc ncargayacn gcnmgntgyw snytnggnyt nwsntgycay 120
ytntgggayg gngaygtnyt ntgyytnccn ggnwsnytnc arwsngcncc nggnccngtn 180
ytngtnccna cnmgnytnca racngarytn gtnytnmgnt gyccncaraa racngaytgy 240
gcnytntgyg tnmgngtngt ngtncayytn gcngtncayg gncaytgggc ngarccngar 300
gargcnggna arwsngayws ngarytncar garwsnmgna aygcnwsnyt ncargcncar 360
gtngtnytnw snttycargc ntayccnath gcnmgntgyg cnytnytnga rgtncargtn 420
ccngcngayy tngtncarcc nggncarwsn gtnggnwsng cngtnttyga ytgyttygar 480
gcnwsnytng gngcngargt ncarathtgg wsntayacna arccnmgnta ycaraargar 540
ytnaayytna cncarcaryt nccngaytgy mgnggnytng argtnmgnga ywsnathcar 600
wsntgytggg tnytnccntg gytnaaygtn wsnacngayg gngayaaygt nytnytnacn 660
ytngaygtnw sngargarca rgayttywsn ttyytnytnt ayytnmgncc ngtnccngay 720
gcnytnaarw snytntggta yaaraayytn acnggnccnc araayathac nytnaaycay 780
acngayytng tnccntgyyt ntgyathcar gtntggwsny tngarccnga ywsngarmgn 840
gtngarttyt gyccnttymg ngargayccn ggngcncaym gnaayytntg gcayathgcn 900
mgnytnmgng tnytnwsncc nggngtntgg carytngayg cnccntgytg yytnccnggn 960
```

```
aargtnacny tntgytggca rgcnccngay carwsnccnt gycarccnyt ngtnccnccn 1020
gtnccncara araaygcnac ngtnaaygar ccncargayt tycarytngt ngcnggncay 1080
ccnaayytnt gygtncargt nwsnacntgg garaargtnc arytncargc ntgyytntgg 1140
gcngaywsny tnggnccntt yaargaygay atgytnytng tngaratgaa racnggnytn 1200
aayaayacnw sngtntgygc nytngarccn wsnggntgya cnccnytncc nwsnatggcn 1260
wsnacnmgng cngcnmgnyt nggngargar ytnytncarg ayttymgnws ncaycartgy 1320
atgcarytnt ggaaygayga yaayatgggn wsnytntggg cntgyccnat ggayaartay 1380
athcaymgnm gntgggtnyt ngtntggytn gcntgyytny tnytngcngc ngcnytntty 1440
ttyttyytny tnytnaaraa rgaymgnmgn aargcngcnm gnggnwsnmg nacngcnytn 1500
ytnytncayw sngcngaygg ngcnggntay garmgnytng tnggngcnyt ngcnwsngcn 1560
ytnwsncara tgccnytnmg ngtngcngtn gayytntggw snmgnmgnga rytnwsngcn 1620
cayggngcny tngcntggtt ycaycaycar mgnmgnmgna thytncarga rggnggngtn 1680
gtnathytny tnttywsncc ngcngcngtn gcncartgyc arcartggyt ncarytncar 1740
acngtngarc cnggnccnca ygaygcnytn gcngcntggy tnwsntgygt nytnccngay 1800
ttyytncarg gnmgngcnac nggnmgntay gtnggngtnt ayttygaygg nytnytncay 1860
ccngaywsng tnccnwsncc nttymgngtn gcnccnytnt tywsnytncc nwsncarytn 1920
ccngcnttyy tngaygcnyt ncarggnggn tgywsnacnw sngcnggnmg nccngcngay 1980
mgngtngarm gngtnacnca rgcnytnmgn wsngcnytng aywsntgyac nwsnwsnwsn 2040
gargcnccng gntgytgyga rgartgggay ytnggnccnt gyacnacnyt ngar       2094
```

Table 3: Nucleotide and polypeptide sequences of DNAX Cytokine Receptor Subunit like embodiments (DCRS8). Primate, e.g., human, embodiment (see SEQ ID NO: 13 and 14). Predicted signal sequence indicated, but may vary by a few positions and depending upon cell type.

```
cccacgcntc cgggccagca gcgggcggcc ggggcgcaga gaacggcctg gctgggcgag 60

cgcacggcc atg gcc ccg tgg ctg cag ctc tgc tcc gtc ttc ttt acg gtc 111
          Met Ala Pro Trp Leu Gln Leu Cys Ser Val Phe Phe Thr Val
              -15                 -10                 -5

aac gcc tgc ctc aac ggc tcg cag ctg gct gtn gcc gct ggc ggg tcc    159
Asn Ala Cys Leu Asn Gly Ser Gln Leu Ala Xaa Ala Ala Gly Gly Ser
     -1   1               5                  10

ggc cgc gcg cng ggc gcc gac acc tgt agc tgg ang gga gtg ggg cca    207
Gly Arg Ala Xaa Gly Ala Asp Thr Cys Ser Trp Xaa Gly Val Gly Pro
 15                  20                  25                  30
```

```
gcc agc aga aac agt ggg ctg tac aac atc acc ttc aaa tat gac aat    255
Ala Ser Arg Asn Ser Gly Leu Tyr Asn Ile Thr Phe Lys Tyr Asp Asn
                 35                  40                  45

tgt acc acc tac ttg aat cca gtg ggg aag cat gtg att gct gac gcc    303
Cys Thr Thr Tyr Leu Asn Pro Val Gly Lys His Val Ile Ala Asp Ala
             50                  55                  60

cag aat atc acc atc agc cag tat gct tgc cat gac caa gtg gca gtc    351
Gln Asn Ile Thr Ile Ser Gln Tyr Ala Cys His Asp Gln Val Ala Val
         65                  70                  75

acc att ctt tgg tcc cca ggg gcc ctc ggc atc gaa ttc ctg aaa gga    399
Thr Ile Leu Trp Ser Pro Gly Ala Leu Gly Ile Glu Phe Leu Lys Gly
     80                  85                  90

ttt cgg gta ata ctg gag gag ctg aag tcg gag gga aga cag ngc caa    447
Phe Arg Val Ile Leu Glu Glu Leu Lys Ser Glu Gly Arg Gln Xaa Gln
 95                 100                 105                 110

caa ctg att cta aag gat ccg aag cag ntc aac agt agc ttc aaa aga    495
Gln Leu Ile Leu Lys Asp Pro Lys Gln Xaa Asn Ser Ser Phe Lys Arg
                115                 120                 125

act gga atg gaa tct caa cct ttn ctg aat atg aaa ttt gaa acg gat    543
Thr Gly Met Glu Ser Gln Pro Xaa Leu Asn Met Lys Phe Glu Thr Asp
            130                 135                 140

tat ttc gta agg ttg tcc ttt tcc ttc att aaa aac gaa agc aat tac    591
Tyr Phe Val Arg Leu Ser Phe Ser Phe Ile Lys Asn Glu Ser Asn Tyr
        145                 150                 155

cac cct ttc ttc ttt aga acc cga gcc tgt gac ctg ttg tta cag ccg    639
His Pro Phe Phe Phe Arg Thr Arg Ala Cys Asp Leu Leu Leu Gln Pro
    160                 165                 170

gac aat cta gct tgt aaa ccc ttc tgg aag cct cgg aac ctg aac atc    687
Asp Asn Leu Ala Cys Lys Pro Phe Trp Lys Pro Arg Asn Leu Asn Ile
175                 180                 185                 190

agc cag cat ggc tcg gac atg cag gtg tcc ttc gac cac gca ccg cac    735
Ser Gln His Gly Ser Asp Met Gln Val Ser Phe Asp His Ala Pro His
                195                 200                 205

aac ttc ggc ttc cgt ttc ttc tat ctt cac tac aag ctc aag cac gaa    783
Asn Phe Gly Phe Arg Phe Phe Tyr Leu His Tyr Lys Leu Lys His Glu
            210                 215                 220

gga cct ttc aag cga aag acc tgt aag cag gag caa act aca gag atg    831
Gly Pro Phe Lys Arg Lys Thr Cys Lys Gln Glu Gln Thr Thr Glu Met
        225                 230                 235

acc agc tgc ctc ctt caa aat gtt tct cca ggg gat tat ata att gag    879
Thr Ser Cys Leu Leu Gln Asn Val Ser Pro Gly Asp Tyr Ile Ile Glu
    240                 245                 250
```

```
ctg gtg gat gac act aac aca aca aga aaa gtg atg cat tat gcc tta    927
Leu Val Asp Asp Thr Asn Thr Thr Arg Lys Val Met His Tyr Ala Leu
255                 260                 265                 270

aag cca gtg cac tcc ccg tgg gcc ggg ccc atc aga gcc gtg gcc atc    975
Lys Pro Val His Ser Pro Trp Ala Gly Pro Ile Arg Ala Val Ala Ile
                275                 280                 285

aca gtg cca ctg gta gtc ata tcg gca ttc gcg acg ctc ttc act gtg    1023
Thr Val Pro Leu Val Val Ile Ser Ala Phe Ala Thr Leu Phe Thr Val
            290                 295                 300

atg tgc cgc aag aag caa caa gaa aat ata tat tca cat tta gat gaa    1071
Met Cys Arg Lys Lys Gln Gln Glu Asn Ile Tyr Ser His Leu Asp Glu
        305                 310                 315

gag agc tct gag tct tcc aca tac act gca gca ctc cca aga gag agg    1119
Glu Ser Ser Glu Ser Ser Thr Tyr Thr Ala Ala Leu Pro Arg Glu Arg
    320                 325                 330

ctc cgg ccg cgg ccg aag gtc ttt ctc tgc tat tcc agt aaa gat ggc    1167
Leu Arg Pro Arg Pro Lys Val Phe Leu Cys Tyr Ser Ser Lys Asp Gly
335                 340                 345                 350

cag aat cac atg aat gtc gtc cag tgt ttc gcc tac ttc ctc cag gac    1215
Gln Asn His Met Asn Val Val Gln Cys Phe Ala Tyr Phe Leu Gln Asp
                355                 360                 365

ttc tgt ggc tgt gag gtg gct ctg gac ctg tgg gaa gac ttc agc ctc    1263
Phe Cys Gly Cys Glu Val Ala Leu Asp Leu Trp Glu Asp Phe Ser Leu
            370                 375                 380

tgt aga gaa ggg cag aga gaa tgg gtc atc cag aag atc cac gag tcc    1311
Cys Arg Glu Gly Gln Arg Glu Trp Val Ile Gln Lys Ile His Glu Ser
        385                 390                 395

cag ttc atc att gtg gtt tgt tcc aaa ggt atg aag tac ttt gtg gac    1359
Gln Phe Ile Ile Val Val Cys Ser Lys Gly Met Lys Tyr Phe Val Asp
    400                 405                 410

aag aag aac tac aaa cac aaa gga ggt ggc cga ggc tcg ggg aaa gga    1407
Lys Lys Asn Tyr Lys His Lys Gly Gly Gly Arg Gly Ser Gly Lys Gly
415                 420                 425                 430

gag ctc ttc ctg gtg gcg gtg tca gcc att gcc gaa aag ctc cgc cag    1455
Glu Leu Phe Leu Val Ala Val Ser Ala Ile Ala Glu Lys Leu Arg Gln
                435                 440                 445

gcc aag cag agt tcg tcc gcg gcg ctc agc aag ttt atc gcc gtc tac    1503
Ala Lys Gln Ser Ser Ser Ala Ala Leu Ser Lys Phe Ile Ala Val Tyr
            450                 455                 460
ttt gat tat tcc tgc gag gga gac gtc ccc ggt atc cta gac ctg agt    1551
Phe Asp Tyr Ser Cys Glu Gly Asp Val Pro Gly Ile Leu Asp Leu Ser
        465                 470                 475

acc aag tac aga ctc atg gac aat ctt cct cag ctc tgt tcc cac ctg    1599
Thr Lys Tyr Arg Leu Met Asp Asn Leu Pro Gln Leu Cys Ser His Leu
    480                 485                 490
```

```
cac tcc cga gac cac ggc ctc cag gag ccg ggg cag cac acg cga cag    1647
His Ser Arg Asp His Gly Leu Gln Glu Pro Gly Gln His Thr Arg Gln
495                 500                 505                 510

ggc agc aga agg aac tac ttc cgg agc aag tca ggc cgg tcc cta tac    1695
Gly Ser Arg Arg Asn Tyr Phe Arg Ser Lys Ser Gly Arg Ser Leu Tyr
                515                 520                 525

gtc gcc att tgc aac atg cac cag ttt att gac gag gag ccc gac tgg    1743
Val Ala Ile Cys Asn Met His Gln Phe Ile Asp Glu Glu Pro Asp Trp
            530                 535                 540

ttc gaa aag cag ttc gtt ccc ttc cat cct cct cca ctg cgc tac cgg    1791
Phe Glu Lys Gln Phe Val Pro Phe His Pro Pro Pro Leu Arg Tyr Arg
        545                 550                 555

gag cca gtc ttg gag aaa ttt gat tcg ggc ttg gtt tta aat gat gtc    1839
Glu Pro Val Leu Glu Lys Phe Asp Ser Gly Leu Val Leu Asn Asp Val
    560                 565                 570

atg tgc aaa cca ggg cct gag agt gac ttc tgc cta aag gta gag gcg    1887
Met Cys Lys Pro Gly Pro Glu Ser Asp Phe Cys Leu Lys Val Glu Ala
575                 580                 585                 590

gct gtt ctt ggg gca acc gga cca gcc gac tcc cag cac gag agt cag    1935
Ala Val Leu Gly Ala Thr Gly Pro Ala Asp Ser Gln His Glu Ser Gln
                595                 600                 605

cat ggg ggc ctg gac caa gac ggg gag gcc cgg cct gcc ctt gac ggt    1983
His Gly Gly Leu Asp Gln Asp Gly Glu Ala Arg Pro Ala Leu Asp Gly
            610                 615                 620

agc gcc gcc ctg caa ccc ctg ctg cac acg gtg aaa gcc ggc agc ccc    2031
Ser Ala Ala Leu Gln Pro Leu Leu His Thr Val Lys Ala Gly Ser Pro
        625                 630                 635

tcg gac atg ccg cgg gac tca ggc atc tat gac tcg tct gtg ccc tca    2079
Ser Asp Met Pro Arg Asp Ser Gly Ile Tyr Asp Ser Ser Val Pro Ser
    640                 645                 650

tcc gag ctg tct ctg cca ctg atg gaa gga ctc tcg acg gac cag aca    2127
Ser Glu Leu Ser Leu Pro Leu Met Glu Gly Leu Ser Thr Asp Gln Thr
655                 660                 665                 670

gaa acg tct tcc ctg acg gag agc gtg tcc tcc tct tca ggc ctg ggt    2175
Glu Thr Ser Ser Leu Thr Glu Ser Val Ser Ser Ser Ser Gly Leu Gly
                675                 680                 685

gag gag gaa cct cct gcc ctt cct tcc aag ctc ctc tct tct ggg tca    2223
Glu Glu Glu Pro Pro Ala Leu Pro Ser Lys Leu Leu Ser Ser Gly Ser
            690                 695                 700

tgc aaa gca gat ctt ggt tgc cgc agc tac act gat gaa ctc cac gcg    2271
Cys Lys Ala Asp Leu Gly Cys Arg Ser Tyr Thr Asp Glu Leu His Ala
        705                 710                 715

gtc gcc cct ttg taacaaaacg aaagagtcta agcattgcca ctttagctgc       2323
Val Ala Pro Leu
    720
```

tgcctccctc tgattcccca gctcatctcc ctggttgcat ggcccacttg gagctgaggt 2383
ctcatacaag gatatttgga gtgaaatgct ggccagtact tgttctccct tgccccaacc 2443
ctttaccgga tatcttgaca aactctccaa ttttctaaaa tgatatggag ctctgaaagg 2503
catgtccata aggtctgaca acagcttgcc aaatttggtt agtccttgga tcagagcctg 2563
ttgtgggagg tagggaggaa atatgtaaag aaaaacagga agatacctgc actaatcatt 2623
cagacttcat tgagctctgc aaactttgcc tgtttgctat tggctacctt gatttgaaat 2683
gctttgtgaa aaaaggcact tttaacatca tagccacaga aatcaagtgc cagtctatct 2743
ggaatccatg ttgtattgca gataatgttc tcatttattt ttg 2786

MAPWLQLCSVFFTVNACLNGSQLAVAAGGSGRAXGADTCSWXGVGPASRNSGLYNITFKYDNCTTYLNPVGK
HVIADAQNITISQYACHDQVAVTILWSPGALGIEFLKGFRVILEELKSEGRQXQQLILKDPKQXNSSFKRTG
MESQPXLNMKFETDYFVRLSFSFIKNESNYHPFFFRTRACDLLLQPDNLACKPFWKPRNLNISQHGSDMQVS
FDHAPHNFGFRFFYLHYKLKHEGPFKRKTCKQEQTTEMTSCLLQNVSPGDYIIELVDDTNTTRKVMHYALKP
VHSPWAGPIRAVAITVPLVVISAFATLFTVMCRKKQQENIYSHLDEESSESSTYTAALPRERLRPRPKVFLC
YSSKDGQNHMNVVQCFAYFLQDFCGCEVALDLWEDFSLCREGQREWVIQKIHESQFIIVVCSKGMKYFVDKK
NYKHKGGGRGSGKGELFLVAVSAIAEKLRQAKQSSSAALSKFIAVYFDYSCEGDVPGILDLSTKYRLMDNLP
QLCSHLHSRDHGLQEPGQHTRQGSRRNYFRSKSGRSLYVAICNMHQFIDEEPDWFEKQFVPFHPPPLRYREP
VLEKFDSGLVLNDVMCKPGPESDFCLKVEAAVLGATGPADSQHESQHGGLDQDGEARPALDGSAALQPLLHT
VKAGSPSDMPRDSGIYDSSVPSSELSLPLMEGLSTDQTETSSLTESVSSSSGLGEEEPPALPSKLLSSGSCK
ADLGCRSYTDELHAVAPL.

Reverse translation of primate, e.g., human, DCRS8 (SEQ ID NO: 15):

atggcnccnt ggytncaryt ntgywsngtn ttyttyacng tnaaygcntg yytnaayggn 60
wsncarytng cngtngcngc nggnggnwsn ggnmgngcnn nnggngcnga yacntgywsn 120
tggnnnggng tnggnccngc nwsnmgnaay wsnggnytnt ayaayathac nttyaartay 180
gayaaytgya cnacntayyt naayccngtn ggnaarcayg tnathgcnga ygcncaraay 240
athacnathw sncartaygc ntgycaygay cargtngcng tnacnathyt ntggwsnccn 300
ggngcnytng gnathgartt yytnaarggn ttymgngtna thytngarga rytnaarwsn 360
garggnmgnc arnnncarca rytnathytn aargayccna arcarnnnaa ywsnwsntty 420
aarmgnacng gnatggarws ncarccnnnn ytnaayatga arttygarac ngaytaytty 480
gtnmgnytnw snttywsntt yathaaraay garwsnaayt aycayccntt yttyttymgn 540
acnmgngcnt gygayytnyt nytncarccn gayaayytng cntgyaarcc nttytggaar 600
ccnmgnaayy tnaayathws ncarcayggn wsngayatgc argtnwsntt ygaycaygcn 660
ccncayaayt tyggnttymg nttyttytay ytncaytaya arytnaarca ygarggnccn 720
ttyaarmgna aracntgyaa rcargarcar acnacngara tgacnwsntg yytnytncar 780
aaygtnwsnc cnggngayta yathathgar ytngtngayg ayacnaayac nacnmgnaar 840

```
gtnatgcayt aygcnytnaa rccngtncay wsnccntggg cnggnccnat hmgngcngtn 900
gcnathacng tnccnytngt ngtnathwsn gcnttygcna cnytnttyac ngtnatgtgy 960
mgnaaraarc arcargaraa yathtaywsn cayytngayg argarwsnws ngarwsnwsn 1020
acntayacng cngcnytncc nmgngarmgn ytnmgnccnm gnccnaargt nttyytntgy 1080
taywsnwsna argayggnca raaycayatg aaygtngtnc artgyttygc ntayttyytn 1140
cargayttyt gyggntgyga rgtngcnytn gayytntggg argayttyws nytntgymgn 1200
garggncarm gngartgggt nathcaraar athcaygarw sncarttyat hathgtngtn 1260
tgywsnaarg gnatgaarta yttygtngay aaraaraayt ayaarcayaa rggnggnggn 1320
mgnggnwsng gnaarggnga rytnttyytn gtngcngtnw sngcnathgc ngaraarytn 1380
mgncargcna arcarwsnws nwsngcngcn ytnwsnaart tyathgcngt ntayttygay 1440
taywsntgyg arggngaygt nccnggnath ytngayytnw snacnaarta ymgnytnatg 1500
gayaayytnc cncarytntg ywsncayytn caywsnmgng aycayggnyt ncargarccn 1560
ggncarcaya cnmgncargg nwsnmgnmgn aaytayttym gnwsnaarws nggnmgnwsn 1620
ytntaygtng cnathtgyaa yatgcaycar ttyathgayg argarccnga ytggttygar 1680
aarcarttyg tnccnttyca yccnccnccn ytnmgntaym gngarccngt nytngaraar 1740
ttygaywsng gnytngtnyt naaygaygtn atgtgyaarc cnggnccnga rwsngaytty 1800
tgyytnaarg tngargcngc ngtnytnggn gcnacnggnc cngcngayws ncarcaygar 1860
wsncarcayg gnggnytnga ycargayggn gargcnmgnc cngcnytnga yggnwsngcn 1920
gcnytncarc cnytnytnca yacngtnaar gcnggnwsnc cnwsngayat gccnmgngay 1980
wsnggnatht aygaywsnws ngtnccnwsn wsngarytnw snytnccnyt natggarggn 2040
ytnwsnacng aycaracnga racnwsnwsn ytnacngarw sngtnwsnws nwsnwsnggn 2100
ytnggngarg argarccncc ngcnytnccn wsnaarytny tnwsnwsngg nwsntgyaar 2160
gcngayytng gntgymgnws ntayacngay garytncayg cngtngcncc nytn       2214
```

Table 4: Nucleotide and polypeptide sequences of DNAX Cytokine Receptor Subunit like embodiments (DCRS9). Primate, e.g., human, embodiment (see SEQ ID NO: 16 and 17). Predicted signal sequence indicated, but may vary by a few positions and depending upon cell type.

```
atg ggg agc tcc aga ctg gca gcc ctg ctc ctg cct ctc ctc ctc ata    48
Met Gly Ser Ser Arg Leu Ala Ala Leu Leu Leu Pro Leu Leu Leu Ile
            -20                 -15                 -10
```

```
gtc atc gac ctc tct gac tct gct ggg att ggc ttt cgc cac ctg ccc    96
Val Ile Asp Leu Ser Asp Ser Ala Gly Ile Gly Phe Arg His Leu Pro
         -5                  -1   1               5

cac tgg aac acc cgc tgt cct ctg gcc tcc cac acg gaa gtt ctg cct   144
His Trp Asn Thr Arg Cys Pro Leu Ala Ser His Thr Glu Val Leu Pro
 10                  15                  20                  25

ata tcc ctt gcc gca cct ggt ggg ccc tct tct cca caa agc ctt ggt   192
Ile Ser Leu Ala Ala Pro Gly Gly Pro Ser Ser Pro Gln Ser Leu Gly
                 30                  35                  40

gtg tgc gag tct ggc act gtt ccc gct gtt tgt gcc agc atc tgc tgt   240
Val Cys Glu Ser Gly Thr Val Pro Ala Val Cys Ala Ser Ile Cys Cys
             45                  50                  55

cag gtg gct cag gtc ttc aac ggg gcc tct tcc acc tcc tgg tgc aga   288
Gln Val Ala Gln Val Phe Asn Gly Ala Ser Ser Thr Ser Trp Cys Arg
         60                  65                  70

aat cca aaa agt ctt cca cat tca agt tct ata gga gac aca aga tgc   336
Asn Pro Lys Ser Leu Pro His Ser Ser Ser Ile Gly Asp Thr Arg Cys
     75                  80                  85

cag cac ctg ctc aga gga agc tgc tgc ctc gtc gtc acc tgt ctg aga   384
Gln His Leu Leu Arg Gly Ser Cys Cys Leu Val Val Thr Cys Leu Arg
 90                  95                 100                 105

aga gcc atc aca ttt cca tcc cct ccc cag aca tct ccc aca agg gac   432
Arg Ala Ile Thr Phe Pro Ser Pro Pro Gln Thr Ser Pro Thr Arg Asp
                110                 115                 120

ttc gct cta aaa gga ccc aac ctt cgg atc cag aga cat ggg aaa gtc   480
Phe Ala Leu Lys Gly Pro Asn Leu Arg Ile Gln Arg His Gly Lys Val
            125                 130                 135

ttc cca gat tgg act cac aaa ggc atg gag gtg ggc act ggg tac aac   528
Phe Pro Asp Trp Thr His Lys Gly Met Glu Val Gly Thr Gly Tyr Asn
        140                 145                 150

agg aga tgg gtt cag ctg agt ggt gga ccc gag ttc tcc ttt gat ttg   576
Arg Arg Trp Val Gln Leu Ser Gly Gly Pro Glu Phe Ser Phe Asp Leu
    155                 160                 165

ctg cct gag gcc cgg gct att cgg gtg acc ata tct tca ggc cct gag   624
Leu Pro Glu Ala Arg Ala Ile Arg Val Thr Ile Ser Ser Gly Pro Glu
170                 175                 180                 185

gtc agc gtg cgt ctt tgt cac cag tgg gca ctg gag tgt gaa gag ctg   672
Val Ser Val Arg Leu Cys His Gln Trp Ala Leu Glu Cys Glu Glu Leu
                190                 195                 200

agc agt ccc tat gat gtc cag aaa att gtg tct ggg ggc cac act gta   720
Ser Ser Pro Tyr Asp Val Gln Lys Ile Val Ser Gly Gly His Thr Val
            205                 210                 215

gag ctg cct tat gaa ttc ctt ctg ccc tgt ctg tgc ata gag gca tcc   768
Glu Leu Pro Tyr Glu Phe Leu Leu Pro Cys Leu Cys Ile Glu Ala Ser
        220                 225                 230
```

```
tac ctg caa gag gac act gtg agg cgc aaa aaa tgt ccc ttc cag agc    816
Tyr Leu Gln Glu Asp Thr Val Arg Arg Lys Lys Cys Pro Phe Gln Ser
    235                 240                 245

tgg cca gaa gcc tat ggc tcg gac ttc tgg aag tca gtg cac ttc act    864
Trp Pro Glu Ala Tyr Gly Ser Asp Phe Trp Lys Ser Val His Phe Thr
250                 255                 260                 265

gac tac agc cag cac act cag atg gtc atg gcc ctg aca ctc cgc tgc    912
Asp Tyr Ser Gln His Thr Gln Met Val Met Ala Leu Thr Leu Arg Cys
                270                 275                 280

cca ctg aag ctg gaa gct gcc ctc tgc cag agg cac gac tgg cat acc    960
Pro Leu Lys Leu Glu Ala Ala Leu Cys Gln Arg His Asp Trp His Thr
            285                 290                 295

ctt tgc aaa gac ctc ccg aat gcc acg gct cga gag tca gat ggg tgg    1008
Leu Cys Lys Asp Leu Pro Asn Ala Thr Ala Arg Glu Ser Asp Gly Trp
        300                 305                 310

tat gtt ttg gag aag gtg gac ctg cac ccc cag ctc tgc ttc aag gta    1056
Tyr Val Leu Glu Lys Val Asp Leu His Pro Gln Leu Cys Phe Lys Val
    315                 320                 325

caa cca tgg ttc tct ttt gga aac agc agc cat gtt gaa tgc ccc cac    1104
Gln Pro Trp Phe Ser Phe Gly Asn Ser Ser His Val Glu Cys Pro His
330                 335                 340                 345

cag act ggg tct ctc aca tcc tgg aat gta agc atg gat acc caa gcc    1152
Gln Thr Gly Ser Leu Thr Ser Trp Asn Val Ser Met Asp Thr Gln Ala
                350                 355                 360

cag cag ctg att ctt cac ttc tcc tca aga atg cat gcc acc ttc agt    1200
Gln Gln Leu Ile Leu His Phe Ser Ser Arg Met His Ala Thr Phe Ser
            365                 370                 375

gct gcc tgg agc ctc cca ggc ttg ggg cag gac act ttg gtg ccc ccc    1248
Ala Ala Trp Ser Leu Pro Gly Leu Gly Gln Asp Thr Leu Val Pro Pro
        380                 385                 390

gtg tac act gtc agc cag gtg tgg cgg tca gat gtc cag ttt gcc tgg    1296
Val Tyr Thr Val Ser Gln Val Trp Arg Ser Asp Val Gln Phe Ala Trp
    395                 400                 405

aag cac ctc ttg tgt cca gat gtc tct tac aga cac ctg ggg ctc ttg    1344
Lys His Leu Leu Cys Pro Asp Val Ser Tyr Arg His Leu Gly Leu Leu
410                 415                 420                 425

atc ctg gca ctg ctg gcc ctc ctc acc cta ctg ggt gtt gtt ctg gcc    1392
Ile Leu Ala Leu Leu Ala Leu Leu Thr Leu Leu Gly Val Val Leu Ala
                430                 435                 440

ctc acc tgc cgg cgc cca cag tca ggc ccg ggc cca gcg cgg cca gtg    1440
Leu Thr Cys Arg Arg Pro Gln Ser Gly Pro Gly Pro Ala Arg Pro Val
            445                 450                 455
```

```
ctc ctc ctg cac gcg gcg gac tcg gag gcg cag cgg cgc ctg gtg gga    1488
Leu Leu Leu His Ala Ala Asp Ser Glu Ala Gln Arg Arg Leu Val Gly
        460                 465                 470

gcg ctg gct gaa ctg cta cgg gca gcg ctg ggc ggc ggg cgc gac gtg    1536
Ala Leu Ala Glu Leu Leu Arg Ala Ala Leu Gly Gly Gly Arg Asp Val
    475                 480                 485

atc gtg gac ctg tgg gag ggg agg cac gtg gcg cgc gtg ggc ccg ctg    1584
Ile Val Asp Leu Trp Glu Gly Arg His Val Ala Arg Val Gly Pro Leu
490                 495                 500                 505

ccg tgg ctc tgg gcg gcg cgg acg cgc gta gcg cgg gag cag ggc act    1632
Pro Trp Leu Trp Ala Ala Arg Thr Arg Val Ala Arg Glu Gln Gly Thr
                510                 515                 520

gtg ctg ctg ctg tgg agc ggc gcc gac ctt cgc ccg gtc agc ggc ccc    1680
Val Leu Leu Leu Trp Ser Gly Ala Asp Leu Arg Pro Val Ser Gly Pro
            525                 530                 535

gac ccc cgc gcc gcg ccc ctg ctc gcc ctg ctc cac gct gcc ccg cgc    1728
Asp Pro Arg Ala Ala Pro Leu Leu Ala Leu Leu His Ala Ala Pro Arg
        540                 545                 550

ccg ctg ctg ctg ctc gct tac ttc agt cgc ctc tgc gcc aag ggc gac    1776
Pro Leu Leu Leu Leu Ala Tyr Phe Ser Arg Leu Cys Ala Lys Gly Asp
    555                 560                 565

atc ccc ccg ccg ctg cgc gcc ctg ccg cgc tac cgc ctg ctg cgc gac    1824
Ile Pro Pro Pro Leu Arg Ala Leu Pro Arg Tyr Arg Leu Leu Arg Asp
570                 575                 580                 585

ctg ccg cgt ctg ctg cgg gcg ctg gac gcg cgg cct ttc gca gag gcc    1872
Leu Pro Arg Leu Leu Arg Ala Leu Asp Ala Arg Pro Phe Ala Glu Ala
                590                 595                 600

acc agc tgg ggc cgc ctt ggg gcg cgg cag cgc agg cag agc cgc cta    1920
Thr Ser Trp Gly Arg Leu Gly Ala Arg Gln Arg Arg Gln Ser Arg Leu
            605                 610                 615

gag ctg tgc agc cgg ctc gaa cga gag gcc gcc cga ctt gca gac cta    1968
Glu Leu Cys Ser Arg Leu Glu Arg Glu Ala Ala Arg Leu Ala Asp Leu
        620                 625                 630

ggt tgagcagagc tccaccgcag tcccgggtgt ctgcggccgc t                  2012
Gly
```

MGSSRLAALLLPLLLIVIDLSDSAGIGFRHLPHWNTRCPLASHTEVLPISLAAPGGPSSPQSLGVCESGTVP
AVCASICCQVAQVFNGASSTSWCRNPKSLPHSSSIGDTRCQHLLRGSCCLVVTCLRRAITFPSPPQTSPTRD
FALKGPNLRIQRHGKVFPDWTHKGMEVGTGYNRRWVQLSGGPEFSFDLLPEARAIRVTISSGPEVSVRLCHQ
WALECEELSSPYDVQKIVSGGHTVELPYEFLLPCLCIEASYLQEDTVRRKKCPFQSWPEAYGSDFWKSVHFT
DYSQHTQMVMALTLRCPLKLEAALCQRHDWHTLCKDLPNATARESDGWYVLEKVDLHPQLCFKVQPWFSFGN
SSHVECPHQTGSLTSWNVSMDTQAQQLILHFSSRMHATFSAAWSLPGLGQDTLVPPVYTVSQVWRSDVQFAW
KHLLCPDVSYRHLGLLILALLALLTLLGVVLALTCRRPQSGPGPARPVLLLHAADSEAQRRLVGALAELLRA
ALGGGRDVIVDLWEGRHVARVGPLPWLWAARTRVAREQGTVLLLWSGADLRPVSGPDPRAAPLLALLHAAPR
PLLLLAYFSRLCAKGDIPPPLRALPRYRLLRDLPRLLRALDARPFAEATSWGRLGARQRRQSRLELCSRLER
EAARLADLG.

Reverse translation of primate, e.g., human, DCRS9 (SEQ ID NO: 18):

```
atgggnwsnw snmgnytngc ngcnytnytn ytnccnytny tnytnathgt nathgayytn 60
wsngaywsng cnggnathgg nttymgncay ytnccncayt ggaayacnmg ntgyccnytn 120
gcnwsncaya cngargtnyt nccnathwsn ytngcngcnc cnggnggncc nwsnwsnccn 180
carwsnytng gngtntgyga rwsnggnacn gtnccngcng tntgygcnws nathtgytgy 240
cargtngcnc argtnttyaa yggngcnwsn wsnacnwsnt ggtgymgnaa yccnaarwsn 300
ytnccncayw snwsnwsnat hggngayacn mgntgycarc ayytnytnmg nggnwsntgy 360
tgyytngtng tnacntgyyt nmgnmgngcn athacnttyc cnwsnccncc ncaracnwsn 420
ccnacnmgng ayttygcnyt naarggnccn aayytnmgna thcarmgnca yggnaargtn 480
ttyccngayt ggacncayaa rggnatggar gtnggnacng gntayaaymg nmgntgggtn 540
carytnwsng gnggnccnga rttywsntty gayytnytnc cngargcnmg ngcnathmgn 600
gtnacnathw snwsnggncc ngargtnwsn gtnmgnytnt gycaycartg ggcnytngar 660
tgygargary tnwsnwsncc ntaygaygtn caraarathg tnwsnggngg ncayacngtn 720
garytnccnt aygarttyyt nytnccntgy ytntgyathg argcnwsnta yytncargar 780
gayacngtnm gnmgnaaraa rtgyccntty carwsntggc cngargcnta yggnwsngay 840
ttytggaarw sngtncaytt yacngaytay wsncarcaya cncaratggt natggcnytn 900
acnytnmgnt gyccnytnaa rytngargcn gcnytntgyc armgncayga ytggcayacn 960
ytntgyaarg ayytnccnaa ygcnacngcn mgngarwsng ayggntggta ygtnytngar 1020
aargtngayy tncayccnca rytntgytty aargtncarc cntggttyws nttyggnaay 1080
wsnwsncayg tngartgycc ncaycaracn ggnwsnytna cnwsntggaa ygtnwsnatg 1140
gayacncarg cncarcaryt nathytncay ttywsnwsnm gnatgcaygc nacnttywsn 1200
gcngcntggw snytnccngg nytnggncar gayacnytng tnccnccngt ntayacngtn 1260
wsncargtnt ggmgnwsnga ygtncartty gcntggaarc ayytnytntg yccngaygtn 1320
wsntaymgnc ayytnggnyt nytnathytn gcnytnytng cnytnytnac nytnytnggn 1380
gtngtnytng cnytnacntg ymgnmgnccn carwsnggnc cnggnccngc nmgnccngtn 1440
ytnytnytnc aygcngcnga ywsngargcn carmgnmgny tngtnggngc nytngcngar 1500
ytnytnmgng cngcnytngg nggnggnmgn gaygtnathg tngayytntg ggarggnmgn 1560
caygtngcnm gngtnggncc nytnccntgg ytntgggcng cnmgnacnmg ngtngcnmgn 1620
garcarggna cngtnytnyt nytntggwsn ggngcngayy tnmgnccngt nwsnggnccn 1680
```

```
gayccnmgng cngcnccnyt nytngcnytn ytncaygcng cnccnmgncc nytnytnytn 1740
ytngcntayt tywsnmgnyt ntgygcnaar ggngayathc cnccnccnyt nmgngcnytn 1800
ccnmgntaym gnytnytnmg ngayytnccn mgnytnytnm gngcnytnga ygcnmgnccn 1860
ttygcngarg cnacnwsntg gggnmgnytn ggngcnmgnc armgnmgnca rwsnmgnytn 1920
garytntgyw snmgnytnga rmgngargcn gcnmgnytng cngayytngg n         1971
```

Rodent, e.g., mouse, embodiment (see SEQ ID NO: 19 and 20). Predicted signal sequence indicated, but may vary by a few positions and depending upon cell type.

```
cagctccggg ccaggccctg ctgccctctt gcagacagga aagacatggt ctctgcgccc 60

tgatcctaca gaagctc atg ggg agc ccc aga ctg gca gcc ttg ctc ctg    110
                   Met Gly Ser Pro Arg Leu Ala Ala Leu Leu Leu
                                -20                 -15

tct ctc ccg cta ctg ctc atc ggc ctc gct gtg tct gct cgg gtt gcc   158
Ser Leu Pro Leu Leu Leu Ile Gly Leu Ala Val Ser Ala Arg Val Ala
        -10                 -5                  -1   1

tgc ccc tgc ctg cgg agt tgg acc agc cac tgt ctc ctg gcc tac cgt   206
Cys Pro Cys Leu Arg Ser Trp Thr Ser His Cys Leu Leu Ala Tyr Arg
  5                  10                  15                  20

gtg gat aaa cgt ttt gct ggc ctt cag tgg ggc tgg ttc cct ctc ttg   254
Val Asp Lys Arg Phe Ala Gly Leu Gln Trp Gly Trp Phe Pro Leu Leu
                 25                  30                  35

gtg agg aaa tct aaa agt cct cct aaa ttt gaa gac tat tgg agg cac   302
Val Arg Lys Ser Lys Ser Pro Pro Lys Phe Glu Asp Tyr Trp Arg His
             40                  45                  50

agg aca cca gca tcc ttc cag agg aag ctg cta ggc agc cct tcc ctg   350
Arg Thr Pro Ala Ser Phe Gln Arg Lys Leu Leu Gly Ser Pro Ser Leu
         55                  60                  65

tct gag gaa agc cat cga att tcc atc ccc tcc tca gcc atc tcc cac   398
Ser Glu Glu Ser His Arg Ile Ser Ile Pro Ser Ser Ala Ile Ser His
     70                  75                  80

aga ggc caa cgc acc aaa agg gcc cag cct tca gct gca gaa gga aga   446
Arg Gly Gln Arg Thr Lys Arg Ala Gln Pro Ser Ala Ala Glu Gly Arg
 85                  90                  95                 100

gaa cat ctc cct gaa gca ggg tca caa aag tgt gga gga cct gaa ttc   494
Glu His Leu Pro Glu Ala Gly Ser Gln Lys Cys Gly Gly Pro Glu Phe
                105                 110                 115

tcc ttt gat ttg ctg ccc gag gtg cag gct gtt cgg gtg act att cct   542
Ser Phe Asp Leu Leu Pro Glu Val Gln Ala Val Arg Val Thr Ile Pro
            120                 125                 130
```

```
gca ggc ccc aag gca cgt gtg cgc ctt tgt tat cag tgg gca ctg gaa    590
Ala Gly Pro Lys Ala Arg Val Arg Leu Cys Tyr Gln Trp Ala Leu Glu
        135                 140                 145

tgt gaa gac ttg agt agc cct ttt gat acc cag aaa att gtg tct gga    638
Cys Glu Asp Leu Ser Ser Pro Phe Asp Thr Gln Lys Ile Val Ser Gly
    150                 155                 160

ggg cac act gta gac ctg cct tat gaa ttc ctt ctg ccc tgc atg tgc    686
Gly His Thr Val Asp Leu Pro Tyr Glu Phe Leu Leu Pro Cys Met Cys
165                 170                 175                 180

ata gag gcc tcc tac ctg caa gag gac act gtg agg cgc aaa agt gtc    734
Ile Glu Ala Ser Tyr Leu Gln Glu Asp Thr Val Arg Arg Lys Ser Val
                185                 190                 195

cct tcc aga gct ggc ctg aag ctt atg gct cag act tct ggc agt caa    782
Pro Ser Arg Ala Gly Leu Lys Leu Met Ala Gln Thr Ser Gly Ser Gln
            200                 205                 210

tac gct tca ctg act aca gcc agc ac                                 808
Tyr Ala Ser Leu Thr Thr Ala Ser
        215                 220
```

```
MGSPRLAALLLSLPLLLIGLAVSARVACPCLRSWTSHCLLAYRVDKRFAGLQWGWFPLLVRKSKSPPKFEDY
WRHRTPASFQRKLLGSPSLSEESHRISIPSSAISHRGQRTKRAQPSAAEGREHLPEAGSQKCGGPEFSFDLL
PEVQAVRVTIPAGPKARVRLCYQWALECEDLSSPFDTQKIVSGGHTVDLPYEFLLPCMCIEASYLQEDTVRR
KSVPSRAGLKLMAQTSGSQYASLTTAS
```

Reverse translation of rodent, e.g., mouse, DCRS9 (SEQ ID NO: 21):

```
atgggnwsnc cnmgnytngc ngcnytnytn ytnwsnytnc cnytnytnyt nathggnytn 60
gcngtnwsng cnmgngtngc ntgyccntgy ytnmgnwsnt ggacnwsnca ytgyytnytn 120
gcntaymgng tngayaarmg nttygcnggn ytncartggg gntggttycc nytnytngtn 180
mgnaarwsna arwsnccncc naarttygar gaytaytggm gncaymgnac nccngcnwsn 240
ttycarmgna arytnytngg nwsnccnwsn ytnwsngarg arwsncaymg nathwsnath 300
ccnwsnwsng cnathwsnca ymgnggncar mgnacnaarm gngcncarcc nwsngcngcn 360
garggnmgng arcayytncc ngargcnggn wsncaraart gyggnggncc ngarttywsn 420
ttygayytny tnccngargt ncargcngtn mgngtnacna thccngcngg nccnaargcn 480
mgngtnmgny tntgytayca rtgggcnytn gartgygarg ayytnwsnws nccnttygay 540
acncaraara thgtnwsngg nggncayacn gtngayytnc cntaygartt yytnytnccn 600
tgyatgtgya thgargcnws ntayytncar gargayacng tnmgnmgnaa rwsngtnccn 660
wsnmgngcng gnytnaaryt natggcncar acnwsnggnw sncartaygc nwsnytnacn 720
acngcnwsn                                                         729
```

Table 5: Nucleotide and polypeptide sequences of DNAX Cytokine Receptor Subunit like embodiments (DCRS10). Primate, e.g., human, embodiment (see SEQ ID NO: 22 and 23).

```
ttttgagcag aggcttccta ggctccgtag aaatttgcat acagcttcca cttcctgctt 60

cagagcctgt tcttctactt acctgggccc ggagaaggtg gagggagacg agaagccgcc 120

gagagccgac taccctccgg gcccagtctg tctgtccgtg gtggatctaa gaaactaga  179

atg aac cga agc att cct gtg gag gtt gat gaa tca gaa cca tac cca   227
Met Asn Arg Ser Ile Pro Val Glu Val Asp Glu Ser Glu Pro Tyr Pro
  1               5                  10                  15

agt cag ttg ctg aaa cca atc cca gaa tat tcc ccg gaa gag gaa tca   275
Ser Gln Leu Leu Lys Pro Ile Pro Glu Tyr Ser Pro Glu Glu Glu Ser
                 20                  25                  30

gaa cca cct gct cca aat ata agg aac atg gca ccc aac agc ttg tct   323
Glu Pro Pro Ala Pro Asn Ile Arg Asn Met Ala Pro Asn Ser Leu Ser
             35                  40                  45

gca ccc aca atg ctt cac aat tcc tcc gga gac ttt tct caa gct cac   371
Ala Pro Thr Met Leu His Asn Ser Ser Gly Asp Phe Ser Gln Ala His
     50                  55                  60

tca acc ctg aaa ctt gca aat cac cag cgg cct gta tcc cgg cag gtc   419
Ser Thr Leu Lys Leu Ala Asn His Gln Arg Pro Val Ser Arg Gln Val
 65                  70                  75                  80

acc tgc ctg cgc act caa gtt ctg gag gac agt gaa gac agt ttc tgc   467
Thr Cys Leu Arg Thr Gln Val Leu Glu Asp Ser Glu Asp Ser Phe Cys
                 85                  90                  95

agg aga cac cca ggc ctg ggc aaa gct ttc cct tct ggg tgc tct gca   515
Arg Arg His Pro Gly Leu Gly Lys Ala Phe Pro Ser Gly Cys Ser Ala
            100                 105                 110

gtc agc gag cct gcg tct gag tct gtg gtt gga gcc ctc cct gca gag   563
Val Ser Glu Pro Ala Ser Glu Ser Val Val Gly Ala Leu Pro Ala Glu
        115                 120                 125

cat cag ttt tca ttt atg gaa aaa cgt aat caa tgg ctg gta tct cag   611
His Gln Phe Ser Phe Met Glu Lys Arg Asn Gln Trp Leu Val Ser Gln
    130                 135                 140

ctt tca gcg gct tct cct gac act ggc cat gac tca gac aaa tca gac   659
Leu Ser Ala Ala Ser Pro Asp Thr Gly His Asp Ser Asp Lys Ser Asp
145                 150                 155                 160

caa agt tta cct aat gcc tca gca gac tcc ttg ggc ggt agc cag gag   707
Gln Ser Leu Pro Asn Ala Ser Ala Asp Ser Leu Gly Gly Ser Gln Glu
                165                 170                 175

atg gtg caa cgg ccc cag cct cac agg aac cga gca ggc ctg gat ctg   755
Met Val Gln Arg Pro Gln Pro His Arg Asn Arg Ala Gly Leu Asp Leu
            180                 185                 190
```

```
cca acc ata gac acg gga tat gat tcc cag ccc cag gat gtc ctg ggc    803
Pro Thr Ile Asp Thr Gly Tyr Asp Ser Gln Pro Gln Asp Val Leu Gly
        195                 200                 205

atc agg cag ctg gaa agg ccc ctg ccc ctc acc tcc gtg tgt tac ccc    851
Ile Arg Gln Leu Glu Arg Pro Leu Pro Leu Thr Ser Val Cys Tyr Pro
    210                 215                 220

cag gac ctc ccc aga cct ctc agg tcc agg gag ttc cct cag ttt gaa    899
Gln Asp Leu Pro Arg Pro Leu Arg Ser Arg Glu Phe Pro Gln Phe Glu
225                 230                 235                 240

cct cag agg tat cca gca tgt gca cag atg ctg cct ccc aat ctt tcc    947
Pro Gln Arg Tyr Pro Ala Cys Ala Gln Met Leu Pro Pro Asn Leu Ser
            245                 250                 255

cca cat gct cca tgg aac tat cat tac cat tgt cct gga agt ccc gat    995
Pro His Ala Pro Trp Asn Tyr His Tyr His Cys Pro Gly Ser Pro Asp
            260                 265                 270

cac cag gtg cca tat ggc cat gac tac cct cga gca gcc tac cag caa    1043
His Gln Val Pro Tyr Gly His Asp Tyr Pro Arg Ala Ala Tyr Gln Gln
        275                 280                 285

gtg atc cag ccg gct ctg cct ggg cag ccc ctg cct gga gcc agt gtg    1091
Val Ile Gln Pro Ala Leu Pro Gly Gln Pro Leu Pro Gly Ala Ser Val
    290                 295                 300

aga ggc ctg cac cct gtg cag aag gtt atc ctg aat tat ccc agc ccc    1139
Arg Gly Leu His Pro Val Gln Lys Val Ile Leu Asn Tyr Pro Ser Pro
305                 310                 315                 320

tgg gac caa gaa gag agg ccc gca cag aga gac tgc tcc ttt ccg ggg    1187
Trp Asp Gln Glu Glu Arg Pro Ala Gln Arg Asp Cys Ser Phe Pro Gly
            325                 330                 335

ctt cca agg cac cag gac cag cca cat cac cag cca cct aat aga gct    1235
Leu Pro Arg His Gln Asp Gln Pro His His Gln Pro Pro Asn Arg Ala
            340                 345                 350

ggt gct cct ggg gag tcc ttg gag tgc cct gca gag ctg aga cca cag    1283
Gly Ala Pro Gly Glu Ser Leu Glu Cys Pro Ala Glu Leu Arg Pro Gln
        355                 360                 365

gtt ccc cag cct ccg tcc cca gct gct gtg cct aga ccc cct agc aac    1331
Val Pro Gln Pro Pro Ser Pro Ala Ala Val Pro Arg Pro Pro Ser Asn
    370                 375                 380

cct cca gcc aga gga act cta aaa aca agc aat ttg cca gaa gaa ttg    1379
Pro Pro Ala Arg Gly Thr Leu Lys Thr Ser Asn Leu Pro Glu Glu Leu
385                 390                 395                 400

cgg aaa gtc ttt atc act tat tcg atg gac aca gct atg gag gtg gtg    1427
Arg Lys Val Phe Ile Thr Tyr Ser Met Asp Thr Ala Met Glu Val Val
            405                 410                 415

aaa ttc gtg aac ttt ttg ttg gta aat ggc ttc caa act gca att gac    1475
Lys Phe Val Asn Phe Leu Leu Val Asn Gly Phe Gln Thr Ala Ile Asp
            420                 425                 430
```

```
ata ttt gag gat aga atc cga ggc att gat atc att aaa tgg atg gag    1523
Ile Phe Glu Asp Arg Ile Arg Gly Ile Asp Ile Ile Lys Trp Met Glu
        435                 440                 445

cgc tac ctt agg gat aag acc gtg atg ata atc gta gca atc agc ccc    1571
Arg Tyr Leu Arg Asp Lys Thr Val Met Ile Ile Val Ala Ile Ser Pro
    450                 455                 460

aaa tac aaa cag gac gtg gaa ggc gct gag tcg cag ctg gac gag gat    1619
Lys Tyr Lys Gln Asp Val Glu Gly Ala Glu Ser Gln Leu Asp Glu Asp
465                 470                 475                 480

gag cat ggc tta cat act aag tac att cat cga atg atg cag att gag    1667
Glu His Gly Leu His Thr Lys Tyr Ile His Arg Met Met Gln Ile Glu
                485                 490                 495

ttc ata aaa caa gga agc atg aat ttc aga ttc atc cct gtg ctc ttc    1715
Phe Ile Lys Gln Gly Ser Met Asn Phe Arg Phe Ile Pro Val Leu Phe
            500                 505                 510

cca aat gct aag aag gag cat gtg ccc acc tgg ctt cag aac act cat    1763
Pro Asn Ala Lys Lys Glu His Val Pro Thr Trp Leu Gln Asn Thr His
        515                 520                 525

gtc tac agc tgg ccc aag aat aaa aaa aac atc ctg ctg cgg ctg ctg    1811
Val Tyr Ser Trp Pro Lys Asn Lys Lys Asn Ile Leu Leu Arg Leu Leu
    530                 535                 540

aga gag gaa gag tat gtg gct cct cca cgg ggg cct ctg ccc acc ctt    1859
Arg Glu Glu Glu Tyr Val Ala Pro Pro Arg Gly Pro Leu Pro Thr Leu
545                 550                 555                 560

cag gtg gtt ccc ttg tgacaccgtt catccccaga tcactgaggc caggccatgt    1914
Gln Val Val Pro Leu
                565

ttggggcctt gttctgacag cattctggct gaggctggtc ggtagcactc ctggctggtt 1974

tttttctgtt cctccccgag aggccctctg gcccccagga aacctgttgt gcagagctct 2034

tccccggaga cctccacaca ccctggcttt gaagtggagt ctgtgactgc tctgcattct 2094

ctgcttttaa aaaaaccatt gcaggtgcca gtgtcccata tgttcctcct gacagtttga 2154

tgtgtccatt ctgggcctct cagtgcttag caagtagata atgtaaggga tgtggcagca 2214

aatggaaatg actacaaaca ctctcctatc aatcacttca ggctactttt atgagttagc 2274

cagatgcttg tgtatcctca gaccaaactg attcatgtac aaataataaa atgtttactc 2334

ttttgtaaaa aaaaaaaaaa aaaaaaaaag aaaaaaaaaa aaa                   2377
```

MNRSIPVEVDESEPYPSQLLKPIPEYSPEEESEPPAPNIRNMAPNSLSAPTMLHNSSGDFSQAHSTLKLANH
QRPVSRQVTCLRTQVLEDSEDSFCRRHPGLGKAFPSGCSAVSEPASESVVGALPAEHQFSFMEKRNQWLVSQ
LSAASPDTGHDSDKSDQSLPNASADSLGGSQEMVQRPQPHRNRAGLDLPTIDTGYDSQPQDVLGIRQLERPL
PLTSVCYPQDLPRPLRSREFPQFEPQRYPACAQMLPPNLSPHAPWNYHYHCPGSPDHQVPYGHDYPRAAYQQ
VIQPALPGQPLPGASVRGLHPVQKVILNYPSPWDQEERPAQRDCSFPGLPRHQDQPHHQPPNRAGAPGESLE
CPAELRPQVPQPPSPAAVPRPPSNPPARGTLKTSNLPEELRKVFITYSMDTAMEVVKFVNFLLVNGFQTAID
IFEDRIRGIDIIKWMERYLRDKTVMIIVAISPKYKQDVEGAESQLDEDEHGLHTKYIHRMMQIEFIKQGSMN
FRFIPVLFPNAKKEHVPTWLQNTHVYSWPKNKKNILLRLLREEEYVAPPRGPLPTLQVVPL

Reverse translation of primate, e.g., human, DCRS10 (SEQ ID NO: 24):

atgaaymgnw snathccngt ngargtngay garwsngarc cntayccnws ncarytnytn 60

aarccnathc cngartayws nccngargar garwsngarc cnccngcncc naayathmgn 120

aayatggcnc cnaaywsnyt nwsngcnccn acnatgytnc ayaaywsnws nggngaytty 180

wsncargcnc aywsnacnyt naarytngcn aaycaycarm gnccngtnws nmgncargtn 240

acntgyytnm gnacncargt nytngargay wsngargayw snttytgymg nmgncayccn 300

ggnytnggna argcnttycc nwsnggntgy wsngcngtnw sngarccngc nwsngarwsn 360

gtngtnggng cnytnccngc ngarcaycar ttywsnttya tggaraarmg naaycartgg 420

ytngtnwsnc arytnwsngc ngcnwsnccn gayacnggnc aygaywsnga yaarwsngay 480

carwsnytnc cnaaygcnws ngcngaywsn ytnggnggnw sncargarat ggtncarmgn 540

ccncarccnc aymgnaaymg ngcnggnytn gayytnccna cnathgayac nggntaygay 600

wsncarccnc argaygtnyt nggnathmgn carytngarm gnccnytncc nytnacnwsn 660

gtntgytayc cncargayyt nccnmgnccn ytnmgnwsnm gngarttycc ncarttygar 720

ccncarmgnt ayccngcntg ygcncaratg ytnccnccna ayytnwsncc ncaygcnccn 780

tggaaytayc aytaycaytg yccnggnwsn ccngaycayc argtnccnta yggncaygay 840

tayccnmgng cngcntayca rcargtnath carccngcny tnccnggnca rccnytnccn 900

ggngcnwsng tnmgnggnyt ncayccngtn caraargtna thytnaayta yccnwsnccn 960

tgggaycarg argarmgncc ngcncarmgn gaytgywsnt tyccnggnyt nccnmgncay 1020

cargaycarc cncaycayca rccnccnaay mgngcnggng cnccnggnga rwsnytngar 1080

tgyccngcng arytnmgncc ncargtnccn carccnccnw snccngcngc ngtnccnmgn 1140

ccnccnwsna ayccnccngc nmgnggnacn ytnaaracnw snaayytncc ngargarytn 1200

mgnaargtnt tyathacnta ywsnatggay acngcnatgg argtngtnaa rttygtnaay 1260

ttyytnytng tnaayggntt ycaracngcn athgayatht tygargaymg nathmgnggn 1320

athgayatha thaartggat ggarmgntay ytnmgngaya aracngtnat gathathgtn 1380

```
gcnathwsnc cnaartayaa rcargaygtn garggngcng arwsncaryt ngaygargay 1440
garcayggny tncayacnaa rtayathcay mgnatgatgc arathgartt yathaarcar 1500
ggnwsnatga ayttymgntt yathccngtn ytnttyccna aygcnaaraa rgarcaygtn 1560
ccnacntggy tncaraayac ncaygtntay wsntggccna araayaaraa raayathytn 1620
ytnmgnytny tnmgngarga rgartaygtn gcnccnccnm gnggnccnyt nccnacnytn 1680
cargtngtnc cnytn                                                  1695
```

Rodent, e.g., mouse, embodiment (see SEQ ID NO: 25 and 26).

```
cag gac ctc cct ggg cct ctg agg tcc agg gaa ttg cca cct cag ttt    48
Gln Asp Leu Pro Gly Pro Leu Arg Ser Arg Glu Leu Pro Pro Gln Phe
 1               5                  10                  15

gaa ctt gag agg tat cca atg aac gcc cag ctg ctg ccg ccc cat cct    96
Glu Leu Glu Arg Tyr Pro Met Asn Ala Gln Leu Leu Pro Pro His Pro
            20                  25                  30

tcc cca cag gcc cca tgg aac tgt cag tac tac tgc ccc gga ggg ccc   144
Ser Pro Gln Ala Pro Trp Asn Cys Gln Tyr Tyr Cys Pro Gly Gly Pro
        35                  40                  45

tac cac cac cag gtg cca cac ggc cat ggc tac cct cca gca gca gcc   192
Tyr His His Gln Val Pro His Gly His Gly Tyr Pro Pro Ala Ala Ala
    50                  55                  60

tac cag caa gta ctc cag cct gct ctg cct ggg cag gtc ctt cct ggg   240
Tyr Gln Gln Val Leu Gln Pro Ala Leu Pro Gly Gln Val Leu Pro Gly
65                  70                  75                  80

gca agg gca aga ggc cca cgc cct gtg cag aag gtc atc ctg aat gac   288
Ala Arg Ala Arg Gly Pro Arg Pro Val Gln Lys Val Ile Leu Asn Asp
                85                  90                  95

tcc agc ccc caa gac caa gaa gag aga cct gca cag aga gac ttc tct   336
Ser Ser Pro Gln Asp Gln Glu Glu Arg Pro Ala Gln Arg Asp Phe Ser
            100                 105                 110

ttc ccg agg ctc ccg agg gac cag ctc tac cgc cca cca tct aat gga   384
Phe Pro Arg Leu Pro Arg Asp Gln Leu Tyr Arg Pro Pro Ser Asn Gly
        115                 120                 125

gtg gaa gcc cct gag gag tcc ttg gac ctt cct gca gag ctg aga cca   432
Val Glu Ala Pro Glu Glu Ser Leu Asp Leu Pro Ala Glu Leu Arg Pro
    130                 135                 140

cat ggt ccc cag gct cca tcc cta gct gcc gtg cct aga ccc cct agc   480
His Gly Pro Gln Ala Pro Ser Leu Ala Ala Val Pro Arg Pro Pro Ser
145                 150                 155                 160

aac ccc tta gcc cga gga act cta aga acc agc aat ttg cca gaa gaa   528
Asn Pro Leu Ala Arg Gly Thr Leu Arg Thr Ser Asn Leu Pro Glu Glu
                165                 170                 175
```

```
tta cgg aaa gtc ttt atc act tat tct atg gac aca gcc atg gag gtg    576
Leu Arg Lys Val Phe Ile Thr Tyr Ser Met Asp Thr Ala Met Glu Val
            180                 185                 190

gtg aaa ttt gtg aac ttt ctg ttg gtg aac ggc ttc caa act gcg att    624
Val Lys Phe Val Asn Phe Leu Leu Val Asn Gly Phe Gln Thr Ala Ile
        195                 200                 205

gac ata ttt gag gat aga atc cgg ggt att gat atc att aaa tgg atg    672
Asp Ile Phe Glu Asp Arg Ile Arg Gly Ile Asp Ile Ile Lys Trp Met
    210                 215                 220

gag cgc tat ctt cga gat aag aca gtg atg ata atc gta gca atc agc    720
Glu Arg Tyr Leu Arg Asp Lys Thr Val Met Ile Ile Val Ala Ile Ser
225                 230                 235                 240

ccc aaa tac aaa cag gat gtg gaa ggc gct gag tcg cag ctg gac gag    768
Pro Lys Tyr Lys Gln Asp Val Glu Gly Ala Glu Ser Gln Leu Asp Glu
                245                 250                 255

gac gag cat ggc tta cat act aag tac att cat cgg atg atg cag att    816
Asp Glu His Gly Leu His Thr Lys Tyr Ile His Arg Met Met Gln Ile
            260                 265                 270

gag ttc ata agt cag gga agc atg aac ttc aga ttc atc cct gtg ctc    864
Glu Phe Ile Ser Gln Gly Ser Met Asn Phe Arg Phe Ile Pro Val Leu
        275                 280                 285

ttc cca aat gcc aag aag gag cat gtg ccg acc tgg ctt cag aac act    912
Phe Pro Asn Ala Lys Lys Glu His Val Pro Thr Trp Leu Gln Asn Thr
    290                 295                 300

cat gtt tac agc tgg ccc aag aat aag aaa aac atc ctg ctg cgg ctg    960
His Val Tyr Ser Trp Pro Lys Asn Lys Lys Asn Ile Leu Leu Arg Leu
305                 310                 315                 320

ctc agg gag gaa gag tat gtg gct cct ccc cga ggc cct ctg ccc acc    1008
Leu Arg Glu Glu Glu Tyr Val Ala Pro Pro Arg Gly Pro Leu Pro Thr
                325                 330                 335

ctt cag gtg gta ccc ttg tgacgatggc cactccagct cagtgccagc           1056
Leu Gln Val Val Pro Leu
            340

ctgttctcac agcattcttc tagcggagct ggctggtggc acccaggccc tggaacacct 1116

cttctacaga gtcctctgtc tcctgagtct gagttgtcct cgctgggctt ccagagcttc 1176

agtgcctgga tgctgcaggt gacagaaaca aacatctatg accacaaaaa ctctcatcac 1236

ttcagctact tttatgagtc ggtcagatgc tctgtgtcct tagaccagtc taaatcatgc 1296

tcaaataata aaatgattat tctttgt                                      1323
```

QDLPGPLRSRELPPQFELERYPMNAQLLPPHPSPQAPWNCQYYCPGGPYHHQVPHGHGYPPAAAYQQVLQPA
LPGQVLPGARARGPRPVQKVILNDSSPQDQEERPAQRDFSFPRLPRDQLYRPPSNGVEAPEESLDLPAELRP
HGPQAPSLAAVPRPPSNPLARGTLRTSNLPEELRKVFITYSMDTAMEVVKFVNFLLVNGFQTAIDIFEDRIR
GIDIIKWMERYLRDKTVMIIVAISPKYKQDVEGAESQLDEDEHGLHTKYIHRMMQIEFISQGSMNFRFIPVL
FPNAKKEHVPTWLQNTHVYSWPKNKKNILLRLLREEEYVAPPRGPLPTLQVVPL.

Reverse translation of rodent, e.g., mouse, DCRS6 (SEQ ID NO: 27):

```
cargayytnc cnggnccnyt nmgnwsnmgn garytnccnc cncarttyga rytngarmgn 60
tayccnatga aygcncaryt nytnccnccn cayccnwsnc cncargcncc ntggaaytgy 120
cartaytayt gyccnggngg nccntaycay caycargtnc cncayggnca yggntayccn 180
ccngcngcng cntaycarca rgtnytncar ccngcnytnc cnggncargt nytnccnggn 240
gcnmgngcnm gnggnccnmg nccngtncar aargtnathy tnaaygayws nwsnccncar 300
gaycargarg armgnccngc ncarmgngay ttywsnttyc cnmgnytncc nmgngaycar 360
ytntaymgnc cnccnwsnaa yggngtngar gcnccngarg arwsnytnga yytnccngcn 420
garytnmgnc cncayggncc ncargcnccn wsnytngcng cngtnccnmg nccnccnwsn 480
aayccnytng cnmgnggnac nytnmgnacn wsnaayytnc cngargaryt nmgnaargtn 540
ttyathacnt aywsnatgga yacngcnatg gargtngtna arttygtnaa yttyytnytn 600
gtnaayggnt tycaracngc nathgayath ttygargaym gnathmgngg nathgayath 660
athaartgga tggarmgnta yytnmgngay aaracngtna tgathathgt ngcnathwsn 720
ccnaartaya arcargaygt ngarggngcn garwsncary tngaygarga ygarcayggn 780
ytncayacna artayathca ymgnatgatg carathgart tyathwsnca rggnwsnatg 840
aayttymgnt tyathccngt nytnttyccn aaygcnaara argarcaygt nccnacntgg 900
ytncaraaya cncaygtnta ywsntggccn aaraayaara araayathyt nytnmgnytn 960
ytnmgngarg argartaygt ngcnccnccn mgnggnccny tnccnacnyt ncargtngtn 1020
ccnytn                                                           1026
```

Table 6: Alignment of the cytoplasmic portions of various cytokine receptor subunits. The IL-17R_Hu (SEQ ID NO: 28) is GenBank AAB99730.1(U58917), gi|7657230; the IL-17R_Mu (SEQ ID NO: 29) is GenBank AAC52357.1(U31993), gi|6680411; the IL-17R_Ce (SEQ ID NO: 30) is GenBank AAA811100.1(U39997), gi|1353171; and the DCRS6_Ce (SEQ ID NO: 31) is EMBCAA90543.1(Z50177), gi|7503597. Of particular interest are motifs or features corresponding, in primate DCRS8 to: R/K at 339/340; D/E at 348/349; alpha helical regions from H353-Q365, C370-S381, E389-H396, K410-D414, and D485-H495; beta sheet regions correspond to F400-V404 and F458-Y462; E at 431; E/D at 442/443; Y/F at 458; D/E at 468-470; Y/F at 481; and Q/R/F at 523.

```
DCRS7_Mu     RTALLLHSADG-AGYERLVGALASALSQMP---LRVAVDLWSRRE-LSAHGALAWFHHQR
DCRS7_Hu     RAALLLYSADD-SGFERLVGALASALCQLP---LRVAVDLWSRRE-LSAQGPVAWFHAQR
IL-17R_Hu    RKVWIIYSADH-PLYVDVVLKFAQFLLTACG--TEVALDLLEEQA-ISEAGVMTWVGRQK
IL-17R_Mu    RKVWIVYSADH-PLYVEVVLKFAQFLITACG--TEVALDLLEEQV-ISEVGVMTWVSRQK
DCRS10       RKVFITYSMD----TAMEVVKFVNFLLVNG---FQTAIDIFEDR--IRGIDIIKWMERYL
DCRS10_Mu    RKVFITYSMD----TAMEVVKFVNFLLVNG---FQTAIDIFEDR--IRGIDIIKWMERYL
DCRS9_Hu     RPVLLLHAADS-EAQRRLVGALAELLRAALGGGRDVIVDLWEGRH-VARVGPLPWLWAAR
DCRS8_Hu     PKVFLCYSSKDGQNHMNVVQCFAYFLQDFCG--CEVALDLWEDFS-LCREGQREWVIQKI
IL-17R_Ce    VKVMIVYADDN-DLHTDCVKKLVENLRNCAS--CDPVFDLEKLI--TAEIVPSRWLVDQI
DCRS6_Hu     IKVLVVYPSEI--CFHHTICYFTEFLQNHCR--SEVILEKWQKKK-IAEMGPVQWLATQK
DCRS6_Ce     FKVMLVCPEVS-GRDEDFMMRIADALKKSN---NKVVCDRWFEDSKNAEENMLHWVYEQT
               . :  .            :  : .  *               :                *.

DCRS7_Mu     RRILQEGGVVILLFSPAAVAQCQ---QWLQLQTVEP---GP---HDALAAWLSCVLPDFL
DCRS7_Hu     RQTLQEGGVVVLLFSPGAVALCS---EWLQDGVSGPGAHGP---HDAFRASLSCVLPDFL
IL-17R_Hu    QEMVESNSKIIVLCSRGTRAKWQALLGRGAP-VRLRCDHGKPV-GDLFTAAMNMILPDFK
IL-17R_Mu    QEMVESNSKIIILCSRGTQAKWKAILGWAEPAVQLRCDHWKPA-GDLFTAAMNMILPDFK
DCRS10       R---DKTVMIIVAISPKYKQDVE----GAESQLDED-EHGL---HTKYIHRM-MQIEFIK
DCRS10_Mu    R---DKTVMIIVAISPKYKQDVE----GAESQLDED-EHGL---HTKYIHRM-MQIEFIS
DCRS9_Hu     TRVAREQGTVLLLWSGADLRPVS----GPDP-RAAP-----------LLA----LLHAAP
DCRS8_Hu     H----ESQFIIVVCSKGMKYFVD---KKNYKHKGGGRGSGK---GELFLVAVSAIAEKLR
IL-17R_Ce    S----SLKKFIIVVSDCAEKILD----TEASETHQLVQARP--FADLFGPAMEMIIRDAT
DCRS6_Hu     K----AADKVVFLLSNDVNSVCD----GTCGKSEGSPSENS---QDLFPLAFNLFCSDLR
DCRS6_Ce     K----IAEKIIVFHSAYYHPRCG---IYDVINNFFPCTDPR-----LAHIALT---PEAQ
                            .:.  *

DCRS7_Mu     QGRATGR-----YVGVYFDGLLHPDSVPSPFRVAPLFSLP-SQLPAFLDALQ--GGCSTS
DCRS7_Hu     QGRAPGS-----YVGACFDRLLHPDAVPALFRTVPVFTLP-SQLPDFLGALQ--QPRAPR
IL-17R_Hu    RPACFGT-----YVVCYFSEVSCDGDVPDLFGAAPRYPLM-DRFEEVYFRIQ--DLEMFQ
IL-17R_Mu    RPACFGT-----YVVCYFSGICSERDVPDLFNITSRYPLM-DRFEEVYFRIQ--DLEMFE
DCRS10       QGSMNFR-----FIPVLFPNAK-KEHVPTWLQNTHVYSWP-KNKKNILLRLL-REEEYVA
DCRS10_Mu    QGSMNFR-----FIPVLFPNAK-KEHVPTWLQNTHVYSWP-KNKKNILLRLL-REEEYVA
DCRS9_Hu     RPL---------LLLAYFSRLCAKGDIPPPLRALPRYRLL-RDLPRLLRALD--ARPFAE
DCRS8_Hu     QAKQSSSAALSKFIAVYFDYSC-EGDVPGILDLSTKYRLM-DNLPQLCSHLHSRDHGLQE
IL-17R_Ce    HNFPEAR---KKYAVVRFNYSP---HVPPNLAILNLPTFIPEQFAQLTAFLHN-VEHTER
DCRS6_Hu     SQIHLHK-----YVVVYFREID-TKDDYNALSVCPKYHLM-KDATAFCAELL---HVKQQ
DCRS6_Ce     RSVPKEV----EYVLPRDQKLL--EDAFDITIADPLVIDIPIEDVAIPENVP--IHHESC

DCRS7_Mu     AGRPADRVER-----VT----QALRSALDSCTS-----------
DCRS7_Hu     SGRLQERAEQ-----VS----RALQPALDSYFHPP---------
IL-17R_Hu    PGRMHRVGELSGDNYLRS---PGGRQLRAALDRFRDWQVRCPDW
IL-17R_Mu    PGRMHHVRELTGDNYLQS---PSGRQLKEAVLRFQEWQTQCPDW
DCRS10       P----PRGPL-----------PTLQVVPL---------------
DCRS10_Mu    P----PRGPL-----------PTLQVVPL---------------
DCRS9_Hu     ATSWGRLGAR-----------QRRQSRLELCSR-----------
DCRS8_Hu     PGQHTRQGSR-----RNYFRSKSGRSLYVAICNMHQFIDEEPDW
IL-17R_Ce    ANVTQNISEA------Q------IHEWNLCASRMMSFFVRNPNW
DCRS6_Hu     VS----AGKR-------------SQACHDGCCSL----------
DCRS6_Ce     DSIDSRNNSK-------------THSTDSGVSSLSS----NS--
```

Table 6 shows comparison of the available sequences of primate, rodent, and various other receptors. Various conserved residues are aligned and indicated. The structually homologous cytoplasmic domains most likely signal through pathways like IL-17, e.g., through NFkB. Similar to IL-1 signalling, it is likely that these receptors are invloved in innate immunity and/or development.

As used herein, the term DCRS shall be used to describe a protein comprising amino acid sequences shown in Tables 1-5, respectively. In many cases, a substantial fragment thereof will be functionally or structurally equivalent, including, e.g., an extracellular or intracellular domain. The invention also includes a protein variation of the respective DCRS allele whose sequence is provided, e.g., a mutein or soluble extracellular construct. Typically, such agonists or antagonists will exhibit less than about 10% sequence differences, and thus will often have between 1 and 11 substitutions, e.g., 2-, 3-, 5-, 7-fold, and others. It also encompasses allelic and other variants, e.g., natural polymorphic, of the protein described. Typically, it will bind to its corresponding biological ligand, perhaps in a dimerized state with an alpha receptor subunit, with high affinity, e.g., at least about 100 nM, usually better than about 30 nM, preferably better than about 10 nM, and more preferably at better than about 3 nM. The term shall also be used herein to refer to related naturally occurring forms, e.g., alleles, polymorphic variants, and metabolic variants of the mammalian protein. Preferred forms of the receptor complexes will bind the appropriate ligand with an affinity and selectivity appropriate for a ligand-receptor interaction.

This invention also encompasses combinations of proteins or peptides having substantial amino acid sequence identity with an amino acid sequence in Tables 1-5. It will include sequence variants with relatively few residue substitutions, e.g., preferably less than about 3-5.

A substantial polypeptide "fragment", or "segment", is a stretch of amino acid residues of at least about 8 amino acids, generally at least 10 amino acids, more generally at least 12 amino acids, often at least 14 amino acids, more often at least 16 amino acids, typically at least 18 amino acids, more typically at least 20 amino acids, usually at least 22 amino acids, more usually at least 24 amino acids, preferably at least 26 amino acids, more preferably at least 28 amino acids, and, in particularly preferred embodiments, at least about 30 or more amino acids. This includes, e.g., 40, 50, 60, 70, 85, 100, 115, 130, 150, and other lengths. Sequences of segments of different proteins can be compared to one another over appropriate length stretches, typically between conserved motifs. In many situations, fragments may exhibit functional properties of the intact subunits, e.g., the extracellular domain of the transmembrane receptor may retain the ligand binding features, and may be used to prepare a soluble receptor-like complex.

Amino acid sequence homology, or sequence identity, is determined by optimizing residue matches. In some comparisons, gaps may be introduces, as required. See, e.g., Needleham, et al., (1970) J. Mol. Biol. 48:443-453; Sankoff, et al., (1983) chapter one in Time Warps, String Edits, and Macromolecules: The Theory and Practice of Sequence Comparison, Addison-Wesley, Reading, MA; and software packages from IntelliGenetics, Mountain View, CA; and the University of Wisconsin Genetics Computer Group (GCG), Madison, WI; each of which is incorporated herein by reference. This changes when considering conservative substitutions as matches. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine. Homologous amino acid sequences are intended to include natural allelic and interspecies variations in the cytokine sequence. Typical homologous proteins or peptides will have from 50-100% homology (if gaps can be introduced), to 60-100% homology (if conservative substitutions are included) with an amino acid sequence segment of, e.g., Table 3 or 4. Homology measures will be at least about 70%, generally at least 76%, more generally at least 81%, often at least 85%, more often at least 88%, typically at least 90%, more typically at least 92%, usually at least 94%, more usually at least 95%, preferably at least 96%, and more preferably at least 97%, and in particularly preferred embodiments, at least 98% or more. The degree of homology will vary with the length of the compared segments. Homologous proteins or peptides, such as the allelic variants, will share most biological activities with the embodiments described in Tables 1-5.

As used herein, the term "biological activity" is used to describe, without limitation, effects on inflammatory responses, innate immunity, and/or morphogenic development by cytokine-like ligands. For example, these receptors should mediate phosphatase or phosphorylase activities, which activities are easily measured by standard procedures. See, e.g., Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 363:736-738. The receptors, or portions thereof, may be useful as phosphate labeling enzymes to label general or specific substrates. The subunits may also be functional immunogens to elicit recognizing antibodies, or antigens capable of binding antibodies.

The terms ligand, agonist, antagonist, and analog of, e.g., a DCRS8 or DCRS9, include molecules that modulate the characteristic cellular responses to cytokine ligand proteins, as well as molecules possessing the more standard structural binding competition features of ligand-receptor interactions, e.g., where the receptor is a natural

receptor or an antibody. The cellular responses likely are typically mediated through receptor tyrosine kinase pathways.

Also, a ligand is a molecule which serves either as a natural ligand to which said receptor, or an analog thereof, binds, or a molecule which is a functional analog of the natural ligand. The functional analog may be a ligand with structural modifications, or may be a wholly unrelated molecule which has a molecular shape which interacts with the appropriate ligand binding determinants. The ligands may serve as agonists or antagonists, see, e.g., Goodman, et al. (eds. 1990) Goodman & Gilman's: The Pharmacological Bases of Therapeutics, Pergamon Press, New York.

Rational drug design may also be based upon structural studies of the molecular shapes of a receptor or antibody and other effectors or ligands. See, e.g., Herz, et al. (1997) J. Recept. Signal Transduct. Res. 17:671-776; and Chaiken, et al. (1996) Trends Biotechnol. 14:369-375. Effectors may be other proteins which mediate other functions in response to ligand binding, or other proteins which normally interact with the receptor. One means for determining which sites interact with specific other proteins is a physical structure determination, e.g., x-ray crystallography or 2 dimensional NMR techniques. These will provide guidance as to which amino acid residues form molecular contact regions. For a detailed description of protein structural determination, see, e.g., Blundell and Johnson (1976) Protein Crystallography, Academic Press, New York, which is hereby incorporated herein by reference.

II. Activities

The cytokine receptor-like proteins will have a number of different biological activities, e.g., modulating cell proliferation, or in phosphate metabolism, being added to or removed from specific substrates, typically proteins. Such will generally result in modulation of an inflammatory function, other innate immunity response, or a morphological effect. The subunit will probably have a specific low affinity binding to the ligand.

The DCRS8 and DCRS9 have characteristic motifs of receptors signaling through the JAK pathway. See, e.g., Ihle, et al. (1997) Stem Cells 15(suppl. 1):105-111; Silvennoinen, et al. (1997) APMIS 105:497-509; Levy (1997) Cytokine Growth Factor Review 8:81-90; Winston and Hunter (1996) Current Biol. 6:668-671; Barrett (1996) Baillieres Clin. Gastroenterol. 10:1-15; and Briscoe, et al. (1996) Philos. Trans. R. Soc. Lond. B. Biol. Sci. 351:167-171.

The biological activities of the cytokine receptor subunits will be related to addition or removal of phosphate moieties to substrates, typically in a specific manner, but occasionally in a non specific manner. Substrates may be identified, or conditions for

enzymatic activity may be assayed by standard methods, e.g., as described in Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 363:736-738.

The receptor subunits may combine to form functional complexes, e.g., which may be useful for binding ligand or preparing antibodies. These will have substantial diagnostic uses, including detection or quantitation.

III. Nucleic Acids

This invention contemplates use of isolated nucleic acid or fragments, e.g., which encode these or closely related proteins, or fragments thereof, e.g., to encode a corresponding polypeptide, preferably one which is biologically active. In addition, this invention covers isolated or recombinant DNAs which encode combinations of such proteins or polypeptides having characteristic sequences, e.g., of the DCRSs. Typically, the nucleic acid is capable of hybridizing, under appropriate conditions, with a nucleic acid sequence segment shown in Tables 1-5, but preferably not with a corresponding segment of other receptors described in Table 6. Said biologically active protein or polypeptide can be a full length protein, or fragment, and will typically have a segment of amino acid sequence highly homologous, e.g., exhibiting significant stretches of identity, to one shown in Tables 1-5. Further, this invention covers the use of isolated or recombinant nucleic acid, or fragments thereof, which encode proteins having fragments which are equivalent to the DCRS8 or DCRS9 proteins. The isolated nucleic acids can have the respective regulatory sequences in the 5' and 3' flanks, e.g., promoters, enhancers, poly-A addition signals, and others from the natural gene. Combinations, as described, are also provided.

An "isolated" nucleic acid is a nucleic acid, e.g., an RNA, DNA, or a mixed polymer, which is substantially pure, e.g., separated from other components which naturally accompany a native sequence, such as ribosomes, polymerases, and flanking genomic sequences from the originating species. The term embraces a nucleic acid sequence which has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates, which are thereby distinguishable from naturally occurring compositions, and chemically synthesized analogs or analogs biologically synthesized by heterologous systems. A substantially pure molecule includes isolated forms of the molecule, either completely or substantially pure.

An isolated nucleic acid will generally be a homogeneous composition of molecules, but will, in some embodiments, contain heterogeneity, preferably minor. This

heterogeneity is typically found at the polymer ends or portions not critical to a desired biological function or activity.

A "recombinant" nucleic acid is typically defined either by its method of production or its structure. In reference to its method of production, e.g., a product made by a process, the process is use of recombinant nucleic acid techniques, e.g., involving human intervention in the nucleotide sequence. Typically this intervention involves in vitro manipulation, although under certain circumstances it may involve more classical animal breeding techniques. Alternatively, it can be a nucleic acid made by generating a sequence comprising fusion of two fragments which are not naturally contiguous to each other, but is meant to exclude products of nature, e.g., naturally occurring mutants as found in their natural state. Thus, for example, products made by transforming cells with an unnaturally occurring vector is encompassed, as are nucleic acids comprising sequence derived using any synthetic oligonucleotide process. Such a process is often done to replace a codon with a redundant codon encoding the same or a conservative amino acid, while typically introducing or removing a restriction enzyme sequence recognition site. Alternatively, the process is performed to join together nucleic acid segments of desired functions to generate a single genetic entity comprising a desired combination of functions not found in the commonly available natural forms, e.g., encoding a fusion protein. Restriction enzyme recognition sites are often the target of such artificial manipulations, but other site specific targets, e.g., promoters, DNA replication sites, regulation sequences, control sequences, or other useful features may be incorporated by design. A similar concept is intended for a recombinant, e.g., fusion, polypeptide. This will include a dimeric repeat. Specifically included are synthetic nucleic acids which, by genetic code redundancy, encode equivalent polypeptides to fragments of DCRSs and fusions of sequences from various different related molecules, e.g., other cytokine receptor family members.

A "fragment" in a nucleic acid context is a contiguous segment of at least about 17 nucleotides, generally at least 21 nucleotides, more generally at least 25 nucleotides, ordinarily at least 30 nucleotides, more ordinarily at least 35 nucleotides, often at least 39 nucleotides, more often at least 45 nucleotides, typically at least 50 nucleotides, more typically at least 55 nucleotides, usually at least 60 nucleotides, more usually at least 66 nucleotides, preferably at least 72 nucleotides, more preferably at least 79 nucleotides, and in particularly preferred embodiments will be at least 85 or more nucleotides. Typically, fragments of different genetic sequences can be compared to one another over appropriate length stretches, particularly defined segments such as the domains described below.

A nucleic acid which codes for the DCRS8 or DCRS9 will be particularly useful to identify genes, mRNA, and cDNA species which code for itself or closely related proteins, as well as DNAs which code for polymorphic, allelic, or other genetic variants, e.g., from different individuals or related species. Preferred probes for such screens are those regions of the interleukin which are conserved between different polymorphic variants or which contain nucleotides which lack specificity, and will preferably be full length or nearly so. In other situations, polymorphic variant specific sequences will be more useful.

This invention further covers recombinant nucleic acid molecules and fragments having a nucleic acid sequence identical to or highly homologous to the isolated DNA set forth herein. In particular, the sequences will often be operably linked to DNA segments which control transcription, translation, and DNA replication. These additional segments typically assist in expression of the desired nucleic acid segment.

Homologous, or highly identical, nucleic acid sequences, when compared to one another, e.g., DCRS8 sequences, exhibit significant similarity. The standards for homology in nucleic acids are either measures for homology generally used in the art by sequence comparison or based upon hybridization conditions. Comparative hybridization conditions are described in greater detail below.

Substantial identity in the nucleic acid sequence comparison context means either that the segments, or their complementary strands, when compared, are identical when optimally aligned, with appropriate nucleotide insertions or deletions, in at least about 60% of the nucleotides, generally at least 66%, ordinarily at least 71%, often at least 76%, more often at least 80%, usually at least 84%, more usually at least 88%, typically at least 91%, more typically at least about 93%, preferably at least about 95%, more preferably at least about 96 to 98% or more, and in particular embodiments, as high at about 99% or more of the nucleotides, including, e.g., segments encoding structural domains such as the segments described below. Alternatively, substantial identity will exist when the segments will hybridize under selective hybridization conditions, to a strand or its complement, typically using a sequence derived from Tables 1-5. Typically, selective hybridization will occur when there is at least about 55% homology over a stretch of at least about 14 nucleotides, more typically at least about 65%, preferably at least about 75%, and more preferably at least about 90%. See, Kanehisa (1984) Nucl. Acids Res. 12:203-213, which is incorporated herein by reference. The length of homology comparison, as described, may be over longer stretches, and in certain embodiments will be over a stretch of at least about 17 nucleotides, generally at least about 20 nucleotides, ordinarily at least about 24 nucleotides, usually at least about 28 nucleotides, typically at least about 32 nucleotides, more typically at least about 40 nucleotides, preferably at least

about 50 nucleotides, and more preferably at least about 75 to 100 or more nucleotides. This includes, e.g., 125, 150, 175, 200, 225, 246, 273, and other lengths.

Stringent conditions, in referring to homology in the hybridization context, will be stringent combined conditions of salt, temperature, organic solvents, and other parameters typically controlled in hybridization reactions. Stringent temperature conditions will usually include temperatures in excess of about 30 C, more usually in excess of about 37 C, typically in excess of about 45 C, more typically in excess of about 55 C, preferably in excess of about 65 C, and more preferably in excess of about 70 C. Stringent salt conditions will ordinarily be less than about 500 mM, usually less than about 400 mM, more usually less than about 300 mM, typically less than about 200 mM, preferably less than about 100 mM, and more preferably less than about 80 mM, even down to less than about 20 mM. However, the combination of parameters is much more important than the measure of any single parameter. See, e.g., Wetmur and Davidson (1968) J. Mol. Biol. 31:349-370, which is hereby incorporated herein by reference.

The isolated DNA can be readily modified by nucleotide substitutions, nucleotide deletions, nucleotide insertions, and inversions of nucleotide stretches. These modifications result in novel DNA sequences which encode this protein or its derivatives. These modified sequences can be used to produce mutant proteins (muteins) or to enhance the expression of variant species. Enhanced expression may involve gene amplification, increased transcription, increased translation, and other mechanisms. Such mutant DCRS8–like derivatives include predetermined or site-specific mutations of the protein or its fragments, including silent mutations using genetic code degeneracy. "Mutant DCRS8" as used herein encompasses a polypeptide otherwise falling within the homology definition of the DCRS8 as set forth above, but having an amino acid sequence which differs from that of other cytokine receptor-like proteins as found in nature, whether by way of deletion, substitution, or insertion. In particular, "site specific mutant DCRS8" encompasses a protein having substantial sequence identity with a protein of Table 3, and typically shares most of the biological activities or effects of the forms disclosed herein.

Although site specific mutation sites are predetermined, mutants need not be site specific. Mammalian DCRS8 mutagenesis can be achieved by making amino acid insertions or deletions in the gene, coupled with expression. Substitutions, deletions, insertions, or many combinations may be generated to arrive at a final construct. Insertions include amino- or carboxy- terminal fusions. Random mutagenesis can be conducted at a target codon and the expressed mammalian DCRS mutants can then be screened for the desired activity, providing some aspect of a structure-activity relationship. Methods for making substitution mutations at predetermined sites in DNA

having a known sequence are well known in the art, e.g., by M13 primer mutagenesis. See also Sambrook, et al. (1989) and Ausubel, et al. (1987 and periodic Supplements).

The mutations in the DNA normally should not place coding sequences out of reading frames and preferably will not create complementary regions that could hybridize to produce secondary mRNA structure such as loops or hairpins.

The phosphoramidite method described by Beaucage and Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce suitable synthetic DNA fragments. A double stranded fragment will often be obtained either by synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Polymerase chain reaction (PCR) techniques can often be applied in mutagenesis. Alternatively, mutagenesis primers are commonly used methods for generating defined mutations at predetermined sites. See, e.g., Innis, et al. (eds. 1990) PCR Protocols: A Guide to Methods and Applications Academic Press, San Diego, CA; and Dieffenbach and Dveksler (1995; eds.) PCR Primer: A Laboratory Manual Cold Spring Harbor Press, CSH, NY.

Certain embodiments of the invention are directed to combination compositions comprising the receptor or ligand sequences described. In other embodiments, functional portions of the sequences may be joined to encode fusion proteins. In other forms, variants of the described sequences may be substituted.

IV. Proteins, Peptides

As described above, the present invention encompasses primate DCRS6-10, e.g., whose sequences are disclosed in Tables 1-5, and described above. Allelic and other variants are also contemplated, including, e.g., fusion proteins combining portions of such sequences with others, including, e.g., epitope tags and functional domains.

The present invention also provides recombinant proteins, e.g., heterologous fusion proteins using segments from these primate or rodent proteins. A heterologous fusion protein is a fusion of proteins or segments which are naturally not normally fused in the same manner. Thus, the fusion product of, e.g., a DCRS8 with another cytokine receptor is a continuous protein molecule having sequences fused in a typical peptide linkage, typically made as a single translation product and exhibiting properties, e.g., sequence or antigenicity, derived from each source peptide. A similar concept applies to heterologous nucleic acid sequences. Combinations of various designated proteins into complexes are also provided.

In addition, new constructs may be made from combining similar functional or structural domains from other related proteins, e.g., cytokine receptors or Toll-like

receptors, including species variants. For example, ligand-binding or other segments may be "swapped" between different new fusion polypeptides or fragments. See, e.g., Cunningham, et al. (1989) Science 243:1330-1336; and O'Dowd, et al. (1988) J. Biol. Chem. 263:15985-15992, each of which is incorporated herein by reference. Thus, new chimeric polypeptides exhibiting new combinations of specificities will result from the functional linkage of receptor-binding specificities. For example, the ligand binding domains from other related receptor molecules may be added or substituted for other domains of this or related proteins. The resulting protein will often have hybrid function and properties. For example, a fusion protein may include a targeting domain which may serve to provide sequestering of the fusion protein to a particular subcellular organelle.

Candidate fusion partners and sequences can be selected from various sequence data bases, e.g., GenBank, c/o IntelliGenetics, Mountain View, CA; and BCG, University of Wisconsin Biotechnology Computing Group, Madison, WI, which are each incorporated herein by reference. In particular, combinations of polypeptide sequences provided in Tables 1-5 are particularly preferred. Variant forms of the proteins may be substituted in the described combinations.

The present invention particularly provides muteins which bind cytokine-like ligands, and/or which are affected in signal transduction. Structural alignment of human DCRSs with other members of the cytokine receptor family show conserved features/residues. See Table 6. Alignment of the human DCRS8 sequence with other members of the cytokine receptor family indicates various structural and functionally shared features. See also, Bazan, et al. (1996) Nature 379:591; Lodi, et al. (1994) Science 263:1762-1766; Sayle and Milner-White (1995) TIBS 20:374-376; and Gronenberg, et al. (1991) Protein Engineering 4:263-269.

Substitutions with either mouse sequences or human sequences are particularly preferred. Conversely, conservative substitutions away from the ligand binding interaction regions will probably preserve most signaling activities; and conservative substitutions away from the intracellular domains will probably preserve most ligand binding properties.

"Derivatives" of the primate DCRS8 include amino acid sequence mutants, glycosylation variants, metabolic derivatives and covalent or aggregative conjugates with other chemical moieties. Covalent derivatives can be prepared by linkage of functionalities to groups which are found in the DCRS8 amino acid side chains or at the N- or C- termini, e.g., by means which are well known in the art. These derivatives can include, without limitation, aliphatic esters or amides of the carboxyl terminus, or of residues containing carboxyl side chains, O-acyl derivatives of hydroxyl group-containing residues, and N-acyl derivatives of the amino terminal amino acid or amino-group

containing residues, e.g., lysine or arginine. Acyl groups are selected from the group of alkyl-moieties, including C3 to C18 normal alkyl, thereby forming alkanoyl aroyl species.

In particular, glycosylation alterations are included, e.g., made by modifying the glycosylation patterns of a polypeptide during its synthesis and processing, or in further processing steps. Particularly preferred means for accomplishing this are by exposing the polypeptide to glycosylating enzymes derived from cells which normally provide such processing, e.g., mammalian glycosylation enzymes. Deglycosylation enzymes are also contemplated. Also embraced are versions of the same primary amino acid sequence which have other minor modifications, including phosphorylated amino acid residues, e.g., phosphotyrosine, phosphoserine, or phosphothreonine.

A major group of derivatives are covalent conjugates of the receptors or fragments thereof with other proteins of polypeptides. These derivatives can be synthesized in recombinant culture such as N- or C-terminal fusions or by the use of agents known in the art for their usefulness in cross-linking proteins through reactive side groups. Preferred derivatization sites with cross-linking agents are at free amino groups, carbohydrate moieties, and cysteine residues.

Fusion polypeptides between the receptors and other homologous or heterologous proteins are also provided. Homologous polypeptides may be fusions between different receptors, resulting in, for instance, a hybrid protein exhibiting binding specificity for multiple different cytokine ligands, or a receptor which may have broadened or weakened specificity of substrate effect. Likewise, heterologous fusions may be constructed which would exhibit a combination of properties or activities of the derivative proteins. Typical examples are fusions of a reporter polypeptide, e.g., luciferase, with a segment or domain of a receptor, e.g., a ligand-binding segment, so that the presence or location of a desired ligand may be easily determined. See, e.g., Dull, et al., U.S. Patent No. 4,859,609, which is hereby incorporated herein by reference. Other gene fusion partners include glutathione-S-transferase (GST), bacterial ß-galactosidase, trpE, Protein A, ß-lactamase, alpha amylase, alcohol dehydrogenase, and yeast alpha mating factor. See, e.g., Godowski, et al. (1988) Science 241:812-816. Labeled proteins will often be substituted in the described combinations of proteins.

The phosphoramidite method described by Beaucage and Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce suitable synthetic DNA fragments. A double stranded fragment will often be obtained either by synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Such polypeptides may also have amino acid residues which have been chemically modified by phosphorylation, sulfonation, biotinylation, or the addition or removal of

other moieties, particularly those which have molecular shapes similar to phosphate groups. In some embodiments, the modifications will be useful labeling reagents, or serve as purification targets, e.g., affinity ligands.

Fusion proteins will typically be made by either recombinant nucleic acid methods or by synthetic polypeptide methods. Techniques for nucleic acid manipulation and expression are described generally, for example, in Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual (2d ed.), Vols. 1-3, Cold Spring Harbor Laboratory, and Ausubel, et al. (eds. 1987 and periodic supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York, which are each incorporated herein by reference. Techniques for synthesis of polypeptides are described, for example, in Merrifield (1963) J. Amer. Chem. Soc. 85:2149-2156; Merrifield (1986) Science 232: 341-347; and Atherton, et al. (1989) Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Oxford; each of which is incorporated herein by reference. See also Dawson, et al. (1994) Science 266:776-779 for methods to make larger polypeptides.

This invention also contemplates the use of derivatives of a DCRS8 other than variations in amino acid sequence or glycosylation. Such derivatives may involve covalent or aggregative association with chemical moieties. These derivatives generally fall into three classes: (1) salts, (2) side chain and terminal residue covalent modifications, and (3) adsorption complexes, for example with cell membranes. Such covalent or aggregative derivatives are useful as immunogens, as reagents in immunoassays, or in purification methods such as for affinity purification of a receptor or other binding molecule, e.g., an antibody. For example, a cytokine ligand can be immobilized by covalent bonding to a solid support such as cyanogen bromide-activated Sepharose, by methods which are well known in the art, or adsorbed onto polyolefin surfaces, with or without glutaraldehyde cross-linking, for use in the assay or purification of a cytokine receptor, antibodies, or other similar molecules. The ligand can also be labeled with a detectable group, for example radioiodinated by the chloramine T procedure, covalently bound to rare earth chelates, or conjugated to another fluorescent moiety for use in diagnostic assays.

A combination, e.g., including a DCRS8, of this invention can be used as an immunogen for the production of antisera or antibodies specific, e.g., capable of distinguishing between other cytokine receptor family members, for the combinations described. The complexes can be used to screen monoclonal antibodies or antigen-binding fragments prepared by immunization with various forms of impure preparations containing the protein. In particular, the term "antibodies" also encompasses antigen binding fragments of natural antibodies, e.g., Fab, Fab2, Fv, etc. The purified DCRS8 can also be used as a reagent to detect antibodies generated in response to the presence of

elevated levels of expression, or immunological disorders which lead to antibody production to the endogenous receptor. Additionally, DCRS8 fragments may also serve as immunogens to produce the antibodies of the present invention, as described immediately below. For example, this invention contemplates antibodies having binding affinity to or being raised against the amino acid sequences shown in Tables 1-5, fragments thereof, or various homologous peptides. In particular, this invention contemplates antibodies having binding affinity to, or having been raised against, specific fragments which are predicted to be, or actually are, exposed at the exterior protein surface of the native DCRS8 or DCRS9. Complexes of combinations of proteins will also be useful, and antibody preparations thereto can be made.

The blocking of physiological response to the receptor ligands may result from the inhibition of binding of the ligand to the receptor, likely through competitive inhibition. Thus, in vitro assays of the present invention will often use antibodies or antigen binding segments of these antibodies, or fragments attached to solid phase substrates. These assays will also allow for the diagnostic determination of the effects of either ligand binding region mutations and modifications, or other mutations and modifications, e.g., which affect signaling or enzymatic function.

This invention also contemplates the use of competitive drug screening assays, e.g., where neutralizing antibodies to the receptor complexes or fragments compete with a test compound for binding to a ligand or other antibody. In this manner, the neutralizing antibodies or fragments can be used to detect the presence of a polypeptide which shares one or more binding sites to a receptor and can also be used to occupy binding sites on a receptor that might otherwise bind a ligand.

V. Making Nucleic Acids and Protein

DNA which encodes the protein or fragments thereof can be obtained by chemical synthesis, screening cDNA libraries, or by screening genomic libraries prepared from a wide variety of cell lines or tissue samples. Natural sequences can be isolated using standard methods and the sequences provided herein, e.g., in Tables 1-5. Other species counterparts can be identified by hybridization techniques, or by various PCR techniques, combined with or by searching in sequence databases, e.g., GenBank.

This DNA can be expressed in a wide variety of host cells for the synthesis of a full-length receptor or fragments which can in turn, for example, be used to generate polyclonal or monoclonal antibodies; for binding studies; for construction and expression of modified ligand binding or kinase/phosphatase domains; and for structure/function studies. Variants or fragments can be expressed in host cells that are transformed or transfected with appropriate expression vectors. These molecules can be substantially

free of protein or cellular contaminants, other than those derived from the recombinant host, and therefore are particularly useful in pharmaceutical compositions when combined with a pharmaceutically acceptable carrier and/or diluent. The protein, or portions thereof, may be expressed as fusions with other proteins. Combinations of the described proteins, or nucleic acids encoding them, are particularly interesting.

Expression vectors are typically self-replicating DNA or RNA constructs containing the desired receptor gene or its fragments, usually operably linked to suitable genetic control elements that are recognized in a suitable host cell. These control elements are capable of effecting expression within a suitable host. The multiple genes may be coordinately expressed, and may be on a polycistronic message. The specific type of control elements necessary to effect expression will depend upon the eventual host cell used. Generally, the genetic control elements can include a prokaryotic promoter system or a eukaryotic promoter expression control system, and typically include a transcriptional promoter, an optional operator to control the onset of transcription, transcription enhancers to elevate the level of mRNA expression, a sequence that encodes a suitable ribosome binding site, and sequences that terminate transcription and translation. Expression vectors also usually contain an origin of replication that allows the vector to replicate independently of the host cell.

The vectors of this invention include those which contain DNA which encodes a combination of proteins, as described, or a biologically active equivalent polypeptide. The DNA can be under the control of a viral promoter and can encode a selection marker. This invention further contemplates use of such expression vectors which are capable of expressing eukaryotic cDNAs coding for such proteins in a prokaryotic or eukaryotic host, where the vector is compatible with the host and where the eukaryotic cDNAs are inserted into the vector such that growth of the host containing the vector expresses the cDNAs in question. Usually, expression vectors are designed for stable replication in their host cells or for amplification to greatly increase the total number of copies of the desirable gene per cell. It is not always necessary to require that an expression vector replicate in a host cell, e.g., it is possible to effect transient expression of the protein or its fragments in various hosts using vectors that do not contain a replication origin that is recognized by the host cell. It is also possible to use vectors that cause integration of the protein encoding portions into the host DNA by recombination.

Vectors, as used herein, comprise plasmids, viruses, bacteriophage, integratable DNA fragments, and other vehicles which enable the integration of DNA fragments into the genome of the host. Expression vectors are specialized vectors which contain genetic control elements that effect expression of operably linked genes. Plasmids are the most commonly used form of vector but all other forms of vectors which serve an equivalent

function and which are, or become, known in the art are suitable for use herein. See, e.g., Pouwels, et al. (1985 and Supplements) Cloning Vectors: A Laboratory Manual, Elsevier, N.Y., and Rodriguez, et al. (eds. 1988) Vectors: A Survey of Molecular Cloning Vectors and Their Uses, Buttersworth, Boston, which are incorporated herein by reference.

Transformed cells are cells, preferably mammalian, that have been transformed or transfected with vectors constructed using recombinant DNA techniques. Transformed host cells usually express the desired proteins, but for purposes of cloning, amplifying, and manipulating its DNA, do not need to express the subject proteins. This invention further contemplates culturing transformed cells in a nutrient medium, thus permitting the proteins to accumulate. The proteins can be recovered, either from the culture or, in certain instances, from the culture medium.

For purposes of this invention, nucleic sequences are operably linked when they are functionally related to each other. For example, DNA for a presequence or secretory leader is operably linked to a polypeptide if it is expressed as a preprotein or participates in directing the polypeptide to the cell membrane or in secretion of the polypeptide. A promoter is operably linked to a coding sequence if it controls the transcription of the polypeptide; a ribosome binding site is operably linked to a coding sequence if it is positioned to permit translation. Usually, operably linked means contiguous and in reading frame, however, certain genetic elements such as repressor genes are not contiguously linked but still bind to operator sequences that in turn control expression.

Suitable host cells include prokaryotes, lower eukaryotes, and higher eukaryotes. Prokaryotes include both gram negative and gram positive organisms, e.g., E. coli and B. subtilis. Lower eukaryotes include yeasts, e.g., S. cerevisiae and Pichia, and species of the genus Dictyostelium. Higher eukaryotes include established tissue culture cell lines from animal cells, both of non-mammalian origin, e.g., insect cells, and birds, and of mammalian origin, e.g., human, primates, and rodents.

Prokaryotic host-vector systems include a wide variety of vectors for many different species. As used herein, E. coli and its vectors will be used generically to include equivalent vectors used in other prokaryotes. A representative vector for amplifying DNA is pBR322 or many of its derivatives. Vectors that can be used to express the receptor or its fragments include, but are not limited to, such vectors as those containing the lac promoter (pUC-series); trp promoter (pBR322-trp); Ipp promoter (the pIN-series); lambda-pP or pR promoters (pOTS); or hybrid promoters such as ptac (pDR540). See Brosius, et al. (1988) "Expression Vectors Employing Lambda-, trp-, lac-, and Ipp-derived Promoters", in Vectors: A Survey of Molecular Cloning Vectors and Their Uses, (eds. Rodriguez and Denhardt), Buttersworth, Boston, Chapter 10, pp. 205-236, which is incorporated herein by reference.

Lower eukaryotes, e.g., yeasts and Dictyostelium, may be transformed with DCRS8 sequence containing vectors. For purposes of this invention, the most common lower eukaryotic host is the baker's yeast, Saccharomyces cerevisiae. It will be used to generically represent lower eukaryotes although a number of other strains and species are also available. Yeast vectors typically consist of a replication origin (unless of the integrating type), a selection gene, a promoter, DNA encoding the receptor or its fragments, and sequences for translation termination, polyadenylation, and transcription termination. Suitable expression vectors for yeast include such constitutive promoters as 3-phosphoglycerate kinase and various other glycolytic enzyme gene promoters or such inducible promoters as the alcohol dehydrogenase 2 promoter or metallothionine promoter. Suitable vectors include derivatives of the following types: self-replicating low copy number (such as the YRp-series), self-replicating high copy number (such as the YEp-series); integrating types (such as the YIp-series), or mini-chromosomes (such as the YCp-series).

Higher eukaryotic tissue culture cells are normally the preferred host cells for expression of the functionally active interleukin or receptor proteins. In principle, many higher eukaryotic tissue culture cell lines are workable, e.g., insect baculovirus expression systems, whether from an invertebrate or vertebrate source. However, mammalian cells are preferred. Transformation or transfection and propagation of such cells has become a routine procedure. Examples of useful cell lines include HeLa cells, Chinese hamster ovary (CHO) cell lines, baby rat kidney (BRK) cell lines, insect cell lines, bird cell lines, and monkey (COS) cell lines. Expression vectors for such cell lines usually include an origin of replication, a promoter, a translation initiation site, RNA splice sites (if genomic DNA is used), a polyadenylation site, and a transcription termination site. These vectors also usually contain a selection gene or amplification gene. Suitable expression vectors may be plasmids, viruses, or retroviruses carrying promoters derived, e.g., from such sources as from adenovirus, SV40, parvoviruses, vaccinia virus, or cytomegalovirus. Representative examples of suitable expression vectors include pCDNA1; pCD, see Okayama, et al. (1985) Mol. Cell Biol. 5:1136-1142; pMC1neo PolyA, see Thomas, et al. (1987) Cell 51:503-512; and a baculovirus vector such as pAC 373 or pAC 610.

For secreted proteins and some membrane proteins, an open reading frame usually encodes a polypeptide that consists of a mature or secreted product covalently linked at its N-terminus to a signal peptide. The signal peptide is cleaved prior to secretion of the mature, or active, polypeptide. The cleavage site can be predicted with a high degree of accuracy from empirical rules, e.g., von-Heijne (1986) Nucleic Acids Research 14:4683-4690; and Nielsen, et al. (1997) Protein Eng. 10:1-12, and the precise amino acid composition of the signal peptide often does not appear to be critical to its function, e.g.,

Randall, et al. (1989) Science 243:1156-1159; and Kaiser, et al. (1987) Science 235:312-317. The mature proteins of the invention can be readily determined using standard methods.

It will often be desired to express these polypeptides in a system which provides a specific or defined glycosylation pattern. In this case, the usual pattern will be that provided naturally by the expression system. However, the pattern will be modifiable by exposing the polypeptide, e.g., an unglycosylated form, to appropriate glycosylating proteins introduced into a heterologous expression system. For example, the receptor gene may be co-transformed with one or more genes encoding mammalian or other glycosylating enzymes. Using this approach, certain mammalian glycosylation patterns will be achievable in prokaryote or other cells. Expression in prokaryote cells will typically lead to unglycosylated forms of protein.

The source of DCRS8 can be a eukaryotic or prokaryotic host expressing recombinant DCRS8, such as is described above. The source can also be a cell line, but other mammalian cell lines are also contemplated by this invention, with the preferred cell line being from the human species.

Now that the sequences are known, the primate DCRS8 or DCRS9, fragments, or derivatives thereof can be prepared by conventional processes for synthesizing peptides. These include processes such as are described in Stewart and Young (1984) Solid Phase Peptide Synthesis, Pierce Chemical Co., Rockford, IL; Bodanszky and Bodanszky (1984) The Practice of Peptide Synthesis, Springer-Verlag, New York; and Bodanszky (1984) The Principles of Peptide Synthesis, Springer-Verlag, New York; all of each which are incorporated herein by reference. For example, an azide process, an acid chloride process, an acid anhydride process, a mixed anhydride process, an active ester process (for example, p-nitrophenyl ester, N-hydroxysuccinimide ester, or cyanomethyl ester), a carbodiimidazole process, an oxidative-reductive process, or a dicyclohexylcarbodiimide (DCCD)/additive process can be used. Solid phase and solution phase syntheses are both applicable to the foregoing processes. Similar techniques can be used with partial DCRS8 or DCRS9 sequences.

The DCRS8 proteins, fragments, or derivatives are suitably prepared in accordance with the above processes as typically employed in peptide synthesis, generally either by a so-called stepwise process which comprises condensing an amino acid to the terminal amino acid, one by one in sequence, or by coupling peptide fragments to the terminal amino acid. Amino groups that are not being used in the coupling reaction typically must be protected to prevent coupling at an incorrect location.

If a solid phase synthesis is adopted, the C-terminal amino acid is bound to an insoluble carrier or support through its carboxyl group. The insoluble carrier is not

particularly limited as long as it has a binding capability to a reactive carboxyl group. Examples of such insoluble carriers include halomethyl resins, such as chloromethyl resin or bromomethyl resin, hydroxymethyl resins, phenol resins, tert-alkyloxycarbonylhydrazidated resins, and the like.

An amino group-protected amino acid is bound in sequence through condensation of its activated carboxyl group and the reactive amino group of the previously formed peptide or chain, to synthesize the peptide step by step. After synthesizing the complete sequence, the peptide is split off from the insoluble carrier to produce the peptide. This solid-phase approach is generally described by Merrifield, et al. (1963) in J. Am. Chem. Soc. 85:2149-2156, which is incorporated herein by reference.

The prepared protein and fragments thereof can be isolated and purified from the reaction mixture by means of peptide separation, e.g., by extraction, precipitation, electrophoresis, various forms of chromatography, and the like. The receptors of this invention can be obtained in varying degrees of purity depending upon desired uses. Purification can be accomplished by use of the protein purification techniques disclosed herein, see below, or by the use of the antibodies herein described in methods of immunoabsorbant affinity chromatography. This immunoabsorbant affinity chromatography is carried out by first linking the antibodies to a solid support and then contacting the linked antibodies with solubilized lysates of appropriate cells, lysates of other cells expressing the receptor, or lysates or supernatants of cells producing the protein as a result of DNA techniques, see below.

Generally, the purified protein will be at least about 40% pure, ordinarily at least about 50% pure, usually at least about 60% pure, typically at least about 70% pure, more typically at least about 80% pure, preferable at least about 90% pure and more preferably at least about 95% pure, and in particular embodiments, 97%-99% or more. Purity will usually be on a weight basis, but can also be on a molar basis. Different assays will be applied as appropriate. Individual proteins may be purified and thereafter combined.

VI. Antibodies

Antibodies can be raised to the various mammalian, e.g., primate DCRS8 or DCRS9 proteins and fragments thereof, both in naturally occurring native forms and in their recombinant forms, the difference being that antibodies to the active receptor are more likely to recognize epitopes which are only present in the native conformations. Denatured antigen detection can also be useful in, e.g., Western analysis. Anti-idiotypic antibodies are also contemplated, which would be useful as agonists or antagonists of a natural receptor or an antibody.

Antibodies, including binding fragments and single chain versions, against predetermined fragments of the protein can be raised by immunization of animals with conjugates of the fragments with immunogenic proteins. Monoclonal antibodies are prepared from cells secreting the desired antibody. These antibodies can be screened for binding to normal or defective protein, or screened for agonistic or antagonistic activity. These monoclonal antibodies will usually bind with at least a K_D of about 1 mM, more usually at least about 300 μM, typically at least about 100μM, more typically at least about 30 μM, preferably at least about 10 μM, and more preferably at least about 3 μM or better.

The antibodies, including antigen binding fragments, of this invention can have significant diagnostic or therapeutic value. They can be potent antagonists that bind to the receptor and inhibit binding to ligand or inhibit the ability of the receptor to elicit a biological response, e.g., act on its substrate. They also can be useful as non-neutralizing antibodies and can be coupled to toxins or radionuclides to bind producing cells, or cells localized to the source of the interleukin. Further, these antibodies can be conjugated to drugs or other therapeutic agents, either directly or indirectly by means of a linker.

The antibodies of this invention can also be useful in diagnostic applications. As capture or non-neutralizing antibodies, they might bind to the receptor without inhibiting ligand or substrate binding. As neutralizing antibodies, they can be useful in competitive binding assays. They will also be useful in detecting or quantifying ligand. They may be used as reagents for Western blot analysis, or for immunoprecipitation or immunopurification of the respective protein. Likewise, nucleic acids and proteins may be immobilized to solid substrates for affinity purification or detection methods. The substrates may be, e.g., solid resin beads or sheets of plastic.

Protein fragments may be joined to other materials, particularly polypeptides, as fused or covalently joined polypeptides to be used as immunogens. Mammalian cytokine receptors and fragments may be fused or covalently linked to a variety of immunogens, such as keyhole limpet hemocyanin, bovine serum albumin, tetanus toxoid, etc. See (1969) Microbiology, Hoeber Medical Division, Harper and Row; Landsteiner (1962) Specificity of Serological Reactions, Dover Publications, New York; and Williams, et al. (1967) Methods in Immunology and Immunochemistry, Vol. 1, Academic Press, New York; each of which is incorporated herein by reference, for descriptions of methods of preparing polyclonal antisera. A typical method involves hyperimmunization of an animal with an antigen. The blood of the animal is then collected shortly after the repeated immunizations and the gamma globulin is isolated.

In some instances, it is desirable to prepare monoclonal antibodies from various mammalian hosts, such as mice, rodents, primates, humans, etc. Description of

techniques for preparing such monoclonal antibodies may be found in, e.g., Stites, et al. (eds.) Basic and Clinical Immunology (4th ed.), Lange Medical Publications, Los Altos, CA, and references cited therein; Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH Press; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed.) Academic Press, New York; and particularly in Kohler and Milstein (1975) Nature 256:495-497, which discusses one method of generating monoclonal antibodies. Each of these references is incorporated herein by reference. Summarized briefly, this method involves injecting an animal with an immunogen. The animal is then sacrificed and cells taken from its spleen, which are then fused with myeloma cells. The result is a hybrid cell or "hybridoma" that is capable of reproducing in vitro. The population of hybridomas is then screened to isolate individual clones, each of which secrete a single antibody species to the immunogen. In this manner, the individual antibody species obtained are the products of immortalized and cloned single B cells from the immune animal generated in response to a specific site recognized on the immunogenic substance.

Other suitable techniques involve in vitro exposure of lymphocytes to the antigenic polypeptides or alternatively to selection of libraries of antibodies in phage or similar vectors. See, Huse, et al. (1989) "Generation of a Large Combinatorial Library of the Immunoglobulin Repertoire in Phage Lambda," Science 246:1275-1281; and Ward, et al. (1989) Nature 341:544-546, each of which is incorporated herein by reference. The polypeptides and antibodies of the present invention may be used with or without modification, including chimeric or humanized antibodies. Frequently, the polypeptides and antibodies will be labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, chemiluminescent moieties, magnetic particles, and the like. Patents, teaching the use of such labels include U.S. Patent Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241. Also, recombinant or chimeric immunoglobulins may be produced, see Cabilly, U.S. Patent No. 4,816,567; or made in transgenic mice, see Mendez, et al. (1997) Nature Genetics 15:146-156; Abgenix; and Medarex. These references are incorporated herein by reference.

The antibodies of this invention can also be used for affinity chromatography in isolating the DCRS8 proteins or peptides. Columns can be prepared where the antibodies are linked to a solid support, e.g., particles, such as agarose, Sephadex, or the like, where a cell lysate may be passed through the column, the column washed, followed by increasing concentrations of a mild denaturant, whereby the purified protein will be

released. Alternatively, the protein may be used to purify antibody. Appropriate cross absorptions or depletions may be applied.

The antibodies may also be used to screen expression libraries for particular expression products. Usually the antibodies used in such a procedure will be labeled with a moiety allowing easy detection of presence of antigen by antibody binding.

Antibodies raised against a cytokine receptor will also be used to raise anti-idiotypic antibodies. These will be useful in detecting or diagnosing various immunological conditions related to expression of the protein or cells which express the protein. They also will be useful as agonists or antagonists of the ligand, which may be competitive inhibitors or substitutes for naturally occurring ligands.

A cytokine receptor protein that specifically binds to or that is specifically immunoreactive with an antibody generated against a defined immunogen, such as an immunogen consisting of the amino acid sequence of SEQ ID NO: 14, is typically determined in an immunoassay. The immunoassay typically uses a polyclonal antiserum which was raised, e.g., to a protein of SEQ ID NO: 14. This antiserum is selected to have low crossreactivity against other cytokine receptor family members, preferably from the same species, and any such crossreactivity is removed by immunoabsorption prior to use in the immunoassay.

In order to produce antisera for use in an immunoassay, the protein, e.g., of SEQ ID NO: 14, is isolated as described herein. For example, recombinant protein may be produced in a mammalian cell line. An appropriate host, e.g., an inbred strain of mice such as Balb/c, is immunized with the selected protein, typically using a standard adjuvant, such as Freund's adjuvant, and a standard mouse immunization protocol (see Harlow and Lane, supra). Alternatively, a synthetic peptide derived from the sequences disclosed herein and conjugated to a carrier protein can be used an immunogen. Polyclonal sera are collected and titered against the immunogen protein in an immunoassay, e.g., a solid phase immunoassay with the immunogen immobilized on a solid support. Polyclonal antisera with a titer of 10^4 or greater are selected and tested for their cross reactivity against other cytokine receptor family members using a competitive binding immunoassay such as the one described in Harlow and Lane, supra, at pages 570-573. Preferably at least two cytokine receptor family members are used in this determination. These cytokine receptor family members can be produced as recombinant proteins and isolated using standard molecular biology and protein chemistry techniques as described herein.

Immunoassays in the competitive binding format can be used for the crossreactivity determinations. For example, the protein of SEQ ID NO: 14 can be immobilized to a solid support. Proteins added to the assay compete with the binding of

the antisera to the immobilized antigen. The ability of the above proteins to compete with the binding of the antisera to the immobilized protein is compared to the other proteins. The percent crossreactivity for the above proteins is calculated, using standard calculations. Those antisera with less than 10% crossreactivity with each of the proteins listed above are selected and pooled. The cross-reacting antibodies are then removed from the pooled antisera by immunoabsorption with the above-listed proteins.

The immunoabsorbed and pooled antisera are then used in a competitive binding immunoassay as described above to compare a second protein to the immunogen protein (e.g., the DCRS8 like protein of SEQ ID NO: 14). In order to make this comparison, the two proteins are each assayed at a wide range of concentrations and the amount of each protein required to inhibit 50% of the binding of the antisera to the immobilized protein is determined. If the amount of the second protein required is less than twice the amount of the protein of the selected protein or proteins that is required, then the second protein is said to specifically bind to an antibody generated to the immunogen.

It is understood that these cytokine receptor proteins are members of a family of homologous proteins that comprise at least 9 so far identified members, 6 mammalian and 3 worm embodiments. For a particular gene product, such as the DCRS8, the term refers not only to the amino acid sequences disclosed herein, but also to other proteins that are allelic, non-allelic, or species variants. It is also understood that the terms include nonnatural mutations introduced by deliberate mutation using conventional recombinant technology such as single site mutation, or by excising short sections of DNA encoding the respective proteins, or by substituting new amino acids, or adding new amino acids. Such minor alterations typically will substantially maintain the immunoidentity of the original molecule and/or its biological activity. Thus, these alterations include proteins that are specifically immunoreactive with a designated naturally occurring DCRS8 protein. The biological properties of the altered proteins can be determined by expressing the protein in an appropriate cell line and measuring the appropriate effect, e.g., upon transfected lymphocytes. Particular protein modifications considered minor would include conservative substitution of amino acids with similar chemical properties, as described above for the cytokine receptor family as a whole. By aligning a protein optimally with the protein of the cytokine receptors and by using the conventional immunoassays described herein to determine immunoidentity, one can determine the protein compositions of the invention.

VII. Kits and quantitation

Both naturally occurring and recombinant forms of the cytokine receptor like molecules of this invention are particularly useful in kits and assay methods. For

example, these methods would also be applied to screening for binding activity, e.g., ligands for these proteins. Several methods of automating assays have been developed in recent years so as to permit screening of tens of thousands of compounds per year. See, e.g., a BIOMEK automated workstation, Beckman Instruments, Palo Alto, California, and Fodor, et al. (1991) Science 251:767-773, which is incorporated herein by reference. The latter describes means for testing binding by a plurality of defined polymers synthesized on a solid substrate. The development of suitable assays to screen for a ligand or agonist/antagonist homologous proteins can be greatly facilitated by the availability of large amounts of purified, soluble cytokine receptors in an active state such as is provided by this invention.

Purified protein can be coated directly onto plates for use in the aforementioned ligand screening techniques. However, non-neutralizing antibodies to these proteins can be used as capture antibodies to immobilize the respective receptor on the solid phase, useful, e.g., in diagnostic uses.

This invention also contemplates use of receptor subunit, fragments thereof, peptides, and their fusion products in a variety of diagnostic kits and methods for detecting the presence of the protein or its ligand. Alternatively, or additionally, antibodies against the molecules may be incorporated into the kits and methods. Typically the kit will have a compartment containing, e.g., a DCRS8 peptide or gene segment or a reagent which recognizes one or the other. Typically, recognition reagents, in the case of peptide, would be a receptor or antibody, or in the case of a gene segment, would usually be a hybridization probe.

A preferred kit for determining the concentration of DCRS8 in a sample would typically comprise a labeled compound, e.g., ligand or antibody, having known binding affinity for DCRS8, a source of DCRS8 (naturally occurring or recombinant) as a positive control, and a means for separating the bound from free labeled compound, e.g., a solid phase for immobilizing the DCRS8 in the test sample. Compartments containing reagents, and instructions, will normally be provided. Appropriate nucleic acid or protein containing kits are also provided.

Antibodies, including antigen binding fragments, specific for mammalian DCRS8 or a peptide fragment, or receptor fragments are useful in diagnostic applications to detect the presence of elevated levels of ligand and/or its fragments. Diagnostic assays may be homogeneous (without a separation step between free reagent and antibody-antigen complex) or heterogeneous (with a separation step). Various commercial assays exist, such as radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), enzyme-multiplied immunoassay technique (EMIT), substrate-labeled fluorescent immunoassay (SLFIA) and the like. For example, unlabeled

antibodies can be employed by using a second antibody which is labeled and which recognizes the antibody to a cytokine receptor or to a particular fragment thereof. These assays have also been extensively discussed in the literature. See, e.g., Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH, and Coligan (ed. 1991 and periodic supplements) Current Protocols In Immunology Greene/Wiley, New York.

Anti-idiotypic antibodies may have similar use to serve as agonists or antagonists of cytokine receptors. These should be useful as therapeutic reagents under appropriate circumstances.

Frequently, the reagents for diagnostic assays are supplied in kits, so as to optimize the sensitivity of the assay. For the subject invention, depending upon the nature of the assay, the protocol, and the label, either labeled or unlabeled antibody, or labeled ligand is provided. This is usually in conjunction with other additives, such as buffers, stabilizers, materials necessary for signal production such as substrates for enzymes, and the like. Preferably, the kit will also contain instructions for proper use and disposal of the contents after use. Typically the kit has compartments for each useful reagent, and will contain instructions for proper use and disposal of reagents. Desirably, the reagents are provided as a dry lyophilized powder, where the reagents may be reconstituted in an aqueous medium having appropriate concentrations for performing the assay.

The aforementioned constituents of the diagnostic assays may be used without modification or may be modified in a variety of ways. For example, labeling may be achieved by covalently or non-covalently joining a moiety which directly or indirectly provides a detectable signal. In many of these assays, a test compound, cytokine receptor, or antibodies thereto can be labeled either directly or indirectly. Possibilities for direct labeling include label groups: radiolabels such as ^{125}I, enzymes (U.S. Pat. No. 3,645,090) such as peroxidase and alkaline phosphatase, and fluorescent labels (U.S. Pat. No. 3,940,475) capable of monitoring the change in fluorescence intensity, wavelength shift, or fluorescence polarization. Both of the patents are incorporated herein by reference. Possibilities for indirect labeling include biotinylation of one constituent followed by binding to avidin coupled to one of the above label groups.

There are also numerous methods of separating the bound from the free ligand, or alternatively the bound from the free test compound. The cytokine receptor can be immobilized on various matrixes followed by washing. Suitable matrices include plastic such as an ELISA plate, filters, and beads. Methods of immobilizing the receptor to a matrix include, without limitation, direct adhesion to plastic, use of a capture antibody, chemical coupling, and biotin-avidin. The last step in this approach involves the precipitation of antibody/antigen complex by any of several methods including those

utilizing, e.g., an organic solvent such as polyethylene glycol or a salt such as ammonium sulfate. Other suitable separation techniques include, without limitation, the fluorescein antibody magnetizable particle method described in Rattle, et al. (1984) Clin. Chem. 30(9):1457-1461, and the double antibody magnetic particle separation as described in U.S. Pat. No. 4,659,678, each of which is incorporated herein by reference.

The methods for linking protein or fragments to various labels have been extensively reported in the literature and do not require detailed discussion here. Many of the techniques involve the use of activated carboxyl groups either through the use of carbodiimide or active esters to form peptide bonds, the formation of thioethers by reaction of a mercapto group with an activated halogen such as chloroacetyl, or an activated olefin such as maleimide, for linkage, or the like. Fusion proteins will also find use in these applications.

Another diagnostic aspect of this invention involves use of oligonucleotide or polynucleotide sequences taken from the sequence of an cytokine receptor. These sequences can be used as probes for detecting levels of the respective cytokine receptor in patients suspected of having an immunological disorder. The preparation of both RNA and DNA nucleotide sequences, the labeling of the sequences, and the preferred size of the sequences has received ample description and discussion in the literature. Normally an oligonucleotide probe should have at least about 14 nucleotides, usually at least about 18 nucleotides, and the polynucleotide probes may be up to several kilobases. Various labels may be employed, most commonly radionuclides, particularly ^{32}P. However, other techniques may also be employed, such as using biotin modified nucleotides for introduction into a polynucleotide. The biotin then serves as the site for binding to avidin or antibodies, which may be labeled with a wide variety of labels, such as radionuclides, fluorescers, enzymes, or the like. Alternatively, antibodies may be employed which can recognize specific duplexes, including DNA duplexes, RNA duplexes, DNA-RNA hybrid duplexes, or DNA-protein duplexes. The antibodies in turn may be labeled and the assay carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected. The use of probes to the novel RNA may be carried out in conventional techniques such as nucleic acid hybridization, plus and minus screening, recombinational probing, hybrid released translation (HRT), and hybrid arrested translation (HART). Antisense nucleic acids, which may be used to block protein expression, are also provided. See, e.g., Isis Pharmaceuticals, Sequitur, Inc., or Hybridon. This also includes amplification techniques such as polymerase chain reaction (PCR).

Diagnostic kits which also test for the qualitative or quantitative presence of other markers are also contemplated. Diagnosis or prognosis may depend on the combination

of multiple indications used as markers. Thus, kits may test for combinations of markers. See, e.g., Viallet, et al. (1989) Progress in Growth Factor Res. 1:89-97.

VIII. Therapeutic Utility

This invention provides reagents with significant therapeutic value. See, e.g., Levitzki (1996) Curr. Opin. Cell Biol. 8:239-244. The cytokine receptors (naturally occurring or recombinant), fragments thereof, mutein receptors, and antibodies, along with compounds identified as having binding affinity to the receptors or antibodies, should be useful in the treatment of conditions exhibiting abnormal expression of the receptors of their ligands. Such abnormality will typically be manifested by immunological disorders, e.g., innate immunity, or developmentally. Additionally, this invention should provide therapeutic value in various diseases or disorders associated with abnormal expression or abnormal triggering of response to the ligand. For example, the IL-1 ligands have been suggested to be involved in morphologic development, e.g., dorso-ventral polarity determination, and immune responses, particularly the primitive innate responses. See, e.g., Sun, et al. (1991) Eur. J. Biochem. 196:247-254; and Hultmark (1994) Nature 367:116-117.

Recombinant cytokine receptors, muteins, agonist or antagonist antibodies thereto, or antibodies can be purified and then administered to a patient. These reagents can be combined for therapeutic use with additional active ingredients, e.g., in conventional pharmaceutically acceptable carriers or diluents, along with physiologically innocuous stabilizers and excipients. These combinations can be sterile, e.g., filtered, and placed into dosage forms as by lyophilization in dosage vials or storage in stabilized aqueous preparations. This invention also contemplates use of antibodies or binding fragments thereof which are not complement binding.

Ligand screening using cytokine receptor or fragments thereof can be performed to identify molecules having binding affinity to the receptors. Subsequent biological assays can then be utilized to determine if a putative ligand can provide competitive binding, which can block intrinsic stimulating activity. Receptor fragments can be used as a blocker or antagonist in that it blocks the activity of ligand. Likewise, a compound having intrinsic stimulating activity can activate the receptor and is thus an agonist in that it simulates the activity of ligand, e.g., inducing signaling. This invention further contemplates the therapeutic use of antibodies to cytokine receptors as antagonists.

The quantities of reagents necessary for effective therapy will depend upon many different factors, including means of administration, target site, reagent physiological life, pharmacological life, physiological state of the patient, and other medicants administered. Thus, treatment dosages should be titrated to optimize safety and efficacy. Typically,

dosages used in vitro may provide useful guidance in the amounts useful for in situ administration of these reagents. Animal testing of effective doses for treatment of particular disorders will provide further predictive indication of human dosage. Various considerations are described, e.g., in Gilman, et al. (eds. 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Penn.; each of which is hereby incorporated herein by reference. Methods for administration are discussed therein and below, e.g., for oral, intravenous, intraperitoneal, or intramuscular administration, transdermal diffusion, and others. Pharmaceutically acceptable carriers will include water, saline, buffers, and other compounds described, e.g., in the Merck Index, Merck & Co., Rahway, New Jersey. Because of the likely high affinity binding, or turnover numbers, between a putative ligand and its receptors, low dosages of these reagents would be initially expected to be effective. And the signaling pathway suggests extremely low amounts of ligand may have effect. Thus, dosage ranges would ordinarily be expected to be in amounts lower than 1 mM concentrations, typically less than about 10 μM concentrations, usually less than about 100 nM, preferably less than about 10 pM (picomolar), and most preferably less than about 1 fM (femtomolar), with an appropriate carrier. Slow release formulations, or slow release apparatus will often be utilized for continuous administration.

Cytokine receptors, fragments thereof, and antibodies or its fragments, antagonists, and agonists, may be administered directly to the host to be treated or, depending on the size of the compounds, it may be desirable to conjugate them to carrier proteins such as ovalbumin or serum albumin prior to their administration. Therapeutic formulations may be administered in many conventional dosage formulations. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. Formulations comprise at least one active ingredient, as defined above, together with one or more acceptable carriers thereof. Each carrier must be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those suitable for oral, rectal, nasal, or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by methods well known in the art of pharmacy. See, e.g., Gilman, et al. (eds. 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Penn.; Avis, et al. (eds. 1993) Pharmaceutical Dosage Forms: Parenteral Medications Dekker, NY; Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Tablets Dekker, NY; and

Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Disperse Systems Dekker, NY. The therapy of this invention may be combined with or used in association with other therapeutic agents, particularly agonists or antagonists of other cytokine receptor family members.

IX. Screening

Drug screening using DCRS8 or fragments thereof can be performed to identify compounds having binding affinity to the receptor subunit, including isolation of associated components. Subsequent biological assays can then be utilized to determine if the compound has intrinsic stimulating activity and is therefore a blocker or antagonist in that it blocks the activity of the ligand. Likewise, a compound having intrinsic stimulating activity can activate the receptor and is thus an agonist in that it simulates the activity of a cytokine ligand. This invention further contemplates the therapeutic use of antibodies to the receptor as cytokine agonists or antagonists.

Similarly, complexes comprising multiple proteins may be used to screen for ligands or reagents capable of recognizing the complex. Most cytokine receptors comprise at least two subunits, which may be the same, or distinct. Alternatively, the transmembrane receptor may bind to a complex comprising a cytokine-like ligand associated with another soluble protein serving, e.g., as a second receptor subunit.

One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant DNA molecules expressing the DCRS8 in combination with another cytokine receptor subunit. Cells may be isolated which express a receptor in isolation from other functional receptors. Such cells, either in viable or fixed form, can be used for standard antibody/antigen or ligand/receptor binding assays. See also, Parce, et al. (1989) Science 246:243-247; and Owicki, et al. (1990) Proc. Nat'l Acad. Sci. USA 87:4007-4011, which describe sensitive methods to detect cellular responses. Competitive assays are particularly useful, where the cells (source of putative ligand) are contacted and incubated with a labeled receptor or antibody having known binding affinity to the ligand, such as ^{125}I-antibody, and a test sample whose binding affinity to the binding composition is being measured. The bound and free labeled binding compositions are then separated to assess the degree of ligand binding. The amount of test compound bound is inversely proportional to the amount of labeled receptor binding to the known source. Many techniques can be used to separate bound from free ligand to assess the degree of ligand binding. This separation step could typically involve a procedure such as adhesion to filters followed by washing, adhesion to plastic followed by washing, or centrifugation of the cell membranes. Viable cells could also be used to screen for the effects of drugs on cytokine mediated functions, e.g., second messenger

levels, e.g., Ca^{++}; cell proliferation; inositol phosphate pool changes; and others. Some detection methods allow for elimination of a separation step, e.g., a proximity sensitive detection system. Calcium sensitive dyes will be useful for detecting Ca^{++} levels, with a fluorimeter or a fluorescence cell sorting apparatus.

X. Ligands

The descriptions of the DCRS8 herein provides means to identify ligands, as described above. Such ligand should bind specifically to the respective receptor with reasonably high affinity. Various constructs are made available which allow either labeling of the receptor to detect its ligand. For example, directly labeling cytokine receptor, fusing onto it markers for secondary labeling, e.g., FLAG or other epitope tags, etc., will allow detection of receptor. This can be histological, as an affinity method for biochemical purification, or labeling or selection in an expression cloning approach. A two-hybrid selection system may also be applied making appropriate constructs with the available cytokine receptor sequences. See, e.g., Fields and Song (1989) Nature 340:245-246.

Most likely candidates will be structually related to members of the IL-17 family. See, e.g., USSN 09/480,287.

The broad scope of this invention is best understood with reference to the following examples, which are not intended to limit the inventions to the specific embodiments.

EXAMPLES

I. General Methods

Some of the standard methods are described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.), vols. 1-3, CSH Press, NY; or Ausubel, et al. (1987 and Supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York. Methods for protein purification include such methods as ammonium sulfate precipitation, column chromatography, electrophoresis, centrifugation, crystallization, and others. See, e.g., Ausubel, et al. (1987 and periodic supplements); Coligan, et al. (ed. 1996) and periodic supplements, Current Protocols In Protein Science Greene/Wiley, New York; Deutscher (1990) "Guide to Protein Purification" in Methods in Enzymology, vol. 182, and other volumes in this series; and manufacturer's literature on use of protein purification products, e.g., Pharmacia, Piscataway, N.J., or Bio-Rad, Richmond, CA. Combination

with recombinant techniques allow fusion to appropriate segments, e.g., to a FLAG sequence or an equivalent which can be fused via a protease-removable sequence. See, e.g., Hochuli (1990) "Purification of Recombinant Proteins with Metal Chelate Absorbent" in Setlow (ed.) Genetic Engineering, Principle and Methods 12:87-98, Plenum Press, N.Y.; and Crowe, et al. (1992) QIAexpress: The High Level Expression & Protein Purification System QUIAGEN, Inc., Chatsworth, CA.

Computer sequence analysis is performed, e.g., using available software programs, including those from the GCG (U. Wisconsin) and GenBank sources. Public sequence databases were also used, e.g., from GenBank and others.

Many techniques applicable to IL-10 receptors may be applied to the DCRSs, as described, e.g., in USSN 08/110,683 (IL-10 receptor), which is incorporated herein by reference.

II. Computational Analysis

Human sequences related to cytokine receptors were identified from genomic sequence database using, e.g., the BLAST server (Altschul, et al. (1994) Nature Genet. 6:119-129). Standard analysis programs may be used to evaluate structure, e.g., PHD (Rost and Sander (1994) Proteins 19:55-72) and DSC (King and Sternberg (1996) Protein Sci. 5:2298-2310). Standard comparison software includes, e.g., Altschul, et al. (1990) J. Mol. Biol. 215:403-10; Waterman (1995) Introduction to Computational Biology: Maps, Sequences, and Genomes Chapman & Hall; Lander and Waterman (eds. 1995) Calculating the Secrets of Life: Applications of the Mathematical Sciences in Molecular Biology National Academy Press; and Speed and Waterman (eds. 1996) Genetic Mapping and DNA Sequencing (IMA Volumes in Mathematics and Its Applications, Vol 81) Springer Verlag. Each reference is incorporate herein by reference.

III. Cloning of full-length cDNAs; Chromosomal localization

PCR primers derived from the sequences are used to probe a human cDNA library. Sequences may be derived, e.g., from Tables 1-5, preferably those adjacent the ends of sequences. Full length cDNAs for primate, rodent, or other species DCRS8 are cloned, e.g., by DNA hybridization screening of λgt10 phage. PCR reactions are conducted using T. aquaticus Taqplus DNA polymerase (Stratagene) under appropriate conditions. Extending partial length cDNA clones is typically routine.

Chromosome spreads are prepared. In situ hybridization is performed on chromosome preparations obtained from phytohemagglutinin-stimulated human lymphocytes cultured for 72 h. 5-bromodeoxyuridine was added for the final seven hours

of culture (60 μg/ml of medium), to ensure a posthybridization chromosomal banding of good quality.

A PCR fragment, amplified with the help of primers, is cloned into an appropriate vector. The vector is labeled by nick-translation with ^3H. The radiolabeled probe is hybridized to metaphase spreads at final concentration of 200 ng/ml of hybridization solution as described, e.g., in Mattei, et al. (1985) Hum. Genet. 69:327-331.

After coating with nuclear track emulsion (KODAK NTB2), slides are exposed. To avoid any slipping of silver grains during the banding procedure, chromosome spreads are first stained with buffered Giemsa solution and metaphase photographed. R-banding is then performed by the fluorochrome-photolysis-Giemsa (FPG) method and metaphases rephotographed before analysis.

Similar appropriate methods are used for other species.

IV. Localization of mRNA

Human multiple tissue (Cat# 1, 2) and cancer cell line blots (Cat# 7757-1), containing approximately 2 μg of poly(A)$^+$ RNA per lane, are purchased from Clontech (Palo Alto, CA). Probes are radiolabeled with [α-^{32}P] dATP, e.g., using the Amersham Rediprime random primer labeling kit (RPN1633). Prehybridization and hybridizations are performed, e.g., at 65° C in 0.5 M Na_2HPO_4, 7% SDS, 0.5 M EDTA (pH 8.0). High stringency washes are conducted, e.g., at 65° C with two initial washes in 2 x SSC, 0.1% SDS for 40 min followed by a subsequent wash in 0.1 x SSC, 0.1% SDS for 20 min. Membranes are then exposed at -70° C to X-Ray film (Kodak) in the presence of intensifying screens. More detailed studies by cDNA library Southerns are performed with selected appropriate human DCRS clones to examine their expression in hemopoietic or other cell subsets.

Alternatively, two appropriate primers are selected from Tables 1-5. RT-PCR is used on an appropriate mRNA sample selected for the presence of message to produce a cDNA, e.g., a sample which expresses the gene.

Full length clones may be isolated by hybridization of cDNA libraries from appropriate tissues pre-selected by PCR signal. Northern blots can be performed.

Message for genes encoding DCRS will be assayed by appropriate technology, e.g., PCR, immunoassay, hybridization, or otherwise. Tissue and organ cDNA preparations are available, e.g., from Clontech, Mountain View, CA. Identification of sources of natural expression are useful, as described. And the identification of functional receptor subunit pairings will allow for prediction of what cells express the combination of receptor subunits which will result in a physiological responsiveness to each of the cytokine ligands.

For mouse counterpart distribution, e.g., Southern Analysis can be performed: DNA (5 μg) from a primary amplified cDNA library was digested with appropriate restriction enzymes to release the inserts, run on a 1% agarose gel and transferred to a nylon membrane (Schleicher and Schuell, Keene, NH).

Samples for mouse mRNA isolation may include: resting mouse fibroblastic L cell line (C200); Braf:ER (Braf fusion to estrogen receptor) transfected cells, control (C201); T cells, TH1 polarized (Mel14 bright, CD4+ cells from spleen, polarized for 7 days with IFN-γ and anti IL-4; T200); T cells, TH2 polarized (Mel14 bright, CD4+ cells from spleen, polarized for 7 days with IL-4 and anti-IFN-γ; T201); T cells, highly TH1 polarized (see Openshaw, et al. (1995) J. Exp. Med. 182:1357-1367; activated with anti-CD3 for 2, 6, 16 h pooled; T202); T cells, highly TH2 polarized (see Openshaw, et al. (1995) J. Exp. Med. 182:1357-1367; activated with anti-CD3 for 2, 6, 16 h pooled; T203); CD44- CD25+ pre T cells, sorted from thymus (T204); TH1 T cell clone D1.1, resting for 3 weeks after last stimulation with antigen (T205); TH1 T cell clone D1.1, 10 μg/ml ConA stimulated 15 h (T206); TH2 T cell clone CDC35, resting for 3 weeks after last stimulation with antigen (T207); TH2 T cell clone CDC35, 10 μg/ml ConA stimulated 15 h (T208); Mel14+ naive T cells from spleen, resting (T209); Mel14+ T cells, polarized to Th1 with IFN-γ/IL-12/anti-IL-4 for 6, 12, 24 h pooled (T210); Mel14+ T cells, polarized to Th2 with IL-4/anti-IFN-γ for 6, 13, 24 h pooled (T211); unstimulated mature B cell leukemia cell line A20 (B200); unstimulated B cell line CH12 (B201); unstimulated large B cells from spleen (B202); B cells from total spleen, LPS activated (B203); metrizamide enriched dendritic cells from spleen, resting (D200); dendritic cells from bone marrow, resting (D201); monocyte cell line RAW 264.7 activated with LPS 4 h (M200); bone-marrow macrophages derived with GM and M-CSF (M201); macrophage cell line J774, resting (M202); macrophage cell line J774 + LPS + anti-IL-10 at 0.5, 1, 3, 6, 12 h pooled (M203); macrophage cell line J774 + LPS + IL-10 at 0.5, 1, 3, 5, 12 h pooled(M204); aerosol challenged mouse lung tissue, Th2 primers, aerosol OVA challenge 7, 14, 23 h pooled (see Garlisi, et al. (1995) Clinical Immunology and Immunopathology 75:75-83; X206); Nippostrongulus-infected lung tissue (see Coffman, et al. (1989) Science 245:308-310; X200); total adult lung, normal (O200); total lung, rag-1 (see Schwarz, et al. (1993) Immunodeficiency 4:249-252; O205); IL-10 K.O. spleen (see Kuhn, et al. (1991) Cell 75:263-274; X201); total adult spleen, normal (O201); total spleen, rag-1 (O207); IL-10 K.O. Peyer's patches (O202); total Peyer's patches, normal (O210); IL-10 K.O. mesenteric lymph nodes (X203); total mesenteric lymph nodes, normal (O211); IL-10 K.O. colon (X203); total colon, normal (O212); NOD mouse pancreas (see Makino, et al. (1980) Jikken Dobutsu 29:1-13; X205); total thymus, rag-1 (O208); total kidney, rag-1 (O209); total heart, rag-1 (O202); total brain, rag-1 (O203);

total testes, rag-1 (O204); total liver, rag-1 (O206); rat normal joint tissue (O300); and rat arthritic joint tissue (X300).

Samples for human mRNA isolation may include, e.g.: peripheral blood mononuclear cells (monocytes, T cells, NK cells, granulocytes, B cells), resting (T100); peripheral blood mononuclear cells, activated with anti-CD3 for 2, 6, 12 h pooled (T101); T cell, TH0 clone Mot 72, resting (T102); T cell, TH0 clone Mot 72, activated with anti-CD28 and anti-CD3 for 3, 6, 12 h pooled (T103); T cell, TH0 clone Mot 72, anergic treated with specific peptide for 2, 7, 12 h pooled (T104); T cell, TH1 clone HY06, resting (T107); T cell, TH1 clone HY06, activated with anti-CD28 and anti-CD3 for 3, 6, 12 h pooled (T108); T cell, TH1 clone HY06, anergic treated with specific peptide for 2, 6, 12 h pooled (T109); T cell, TH2 clone HY935, resting (T110); T cell, TH2 clone HY935, activated with anti-CD28 and anti-CD3 for 2, 7, 12 h pooled (T111); T cells CD4+CD45RO- T cells polarized 27 days in anti-CD28, IL-4, and anti IFN-γ, TH2 polarized, activated with anti-CD3 and anti-CD28 4 h (T116); T cell tumor lines Jurkat and Hut78, resting (T117); T cell clones, pooled AD130.2, Tc783.12, Tc783.13, Tc783.58, Tc782.69, resting (T118); T cell random γδ T cell clones, resting (T119); Splenocytes, resting (B100); Splenocytes, activated with anti-CD40 and IL-4 (B101); B cell EBV lines pooled WT49, RSB, JY, CVIR, 721.221, RM3, HSY, resting (B102); B cell line JY, activated with PMA and ionomycin for 1, 6 h pooled (B103); NK 20 clones pooled, resting (K100); NK 20 clones pooled, activated with PMA and ionomycin for 6 h (K101); NKL clone, derived from peripheral blood of LGL leukemia patient, IL-2 treated (K106); NK cytotoxic clone 640-A30-1, resting (K107); hematopoietic precursor line TF1, activated with PMA and ionomycin for 1, 6 h pooled (C100); U937 premonocytic line, resting (M100); U937 premonocytic line, activated with PMA and ionomycin for 1, 6 h pooled (M101); elutriated monocytes, activated with LPS, IFNγ, anti-IL-10 for 1, 2, 6, 12, 24 h pooled (M102); elutriated monocytes, activated with LPS, IFNγ, IL-10 for 1, 2, 6, 12, 24 h pooled (M103); elutriated monocytes, activated with LPS, IFNγ, anti-IL-10 for 4, 16 h pooled (M106); elutriated monocytes, activated with LPS, IFNγ, IL-10 for 4, 16 h pooled (M107); elutriated monocytes, activated LPS for 1 h (M108); elutriated monocytes, activated LPS for 6 h (M109); DC 70% CD1a+, from CD34+ GM-CSF, TNFα 12 days, resting (D101); DC 70% CD1a+, from CD34+ GM-CSF, TNFα 12 days, activated with PMA and ionomycin for 1 hr (D102); DC 70% CD1a+, from CD34+ GM-CSF, TNFα 12 days, activated with PMA and ionomycin for 6 hr (D103); DC 95% CD1a+, from CD34+ GM-CSF, TNFα 12 days FACS sorted, activated with PMA and ionomycin for 1, 6 h pooled (D104); DC 95% CD14+, ex CD34+ GM-CSF, TNFα 12 days FACS sorted, activated with PMA and ionomycin 1, 6 hr pooled (D105); DC CD1a+ CD86+, from CD34+ GM-CSF, TNFα 12 days FACS sorted, activated with PMA and

ionomycin for 1, 6 h pooled (D106); DC from monocytes GM-CSF, IL-4 5 days, resting (D107); DC from monocytes GM-CSF, IL-4 5 days, resting (D108); DC from monocytes GM-CSF, IL-4 5 days, activated LPS 4, 16 h pooled (D109); DC from monocytes GM-CSF, IL-4 5 days, activated TNFα, monocyte supe for 4, 16 h pooled (D110); leiomyoma L11 benign tumor (X101); normal myometrium M5 (O115); malignant leiomyosarcoma GS1 (X103); lung fibroblast sarcoma line MRC5, activated with PMA and ionomycin for 1, 6 h pooled (C101); kidney epithelial carcinoma cell line CHA, activated with PMA and ionomycin for 1, 6 h pooled (C102); kidney fetal 28 wk male (O100); lung fetal 28 wk male (O101); liver fetal 28 wk male (O102); heart fetal 28 wk male (O103); brain fetal 28 wk male (O104); gallbladder fetal 28 wk male (O106); small intestine fetal 28 wk male (O107); adipose tissue fetal 28 wk male (O108); ovary fetal 25 wk female (O109); uterus fetal 25 wk female (O110); testes fetal 28 wk male (O111); spleen fetal 28 wk male (O112); adult placenta 28 wk (O113); and tonsil inflamed, from 12 year old (X100).

TaqMan quantitative PCR techniques have shown the DCRS6, in both mouse and human, to be expressed on T cells, including thymocytes and CD4+ naive and differentiated (hDCRS6 is also expressed on dendritic cells), in gastrointestinal tissue, including stomach, intestine, colon and associated lymphoid tissue, e.g., Peyer's patches and mesenteric lymph nodes, and upregulated in inflammatory models of bowel disease, e.g., IL-10 KO mice. The hDCRS7 was detected in both resting and activated dendritic cells, epithelial cells, and mucosal tissues, including GI and reproductive tracts. These data suggest that family members are expressed in mucosal tissues and immune system cell types, and/or in gastrointestinal, airway, and reproductive tract development.

As such, therapeutic indications include, e.g., short bowel syndrome, post chemo/radio-therapy or alcoholic recovery, combinations with ulcer treatments or arthritis medication, Th2 pregnancy skewing, stomach lining/tissue regeneration, loss of adsorptive surface conditions, etc. See, e.g., Yamada, et al. (eds. 1999) Textbook of Gastroenterology; Yamada, et al. (eds. 1999) Textbook and Atlas of Gastroenterology; Gore and Levine (2000) Textbook of Gastrointestinal Radiology; and (1987) Textbook of Pediatric Gastroenterology.

Similar samples may isolated in other species for evaluation.

Primers specific for IL-17RA were designed and used in Taqman quantative PCR against various human libraries. IL-17RA is highly expressed in innate immune myeloid cells including dendritic cells and monocytes. Expression is also detected in T-cell libraries. These data demonstrate the receptor is expressed in immune cell types and may be regulated by activation conditions.

Table for IL-17RA

library description	CT for IL-17RA_H
DC ex monocytes GM-CSF, IL-4, resting	16.97
U937 premonocytic line, activated	17.14
DC ex monocytes GM-CSF, IL-4, resting	17.53
DC 70% CD1a+, ex CD34+ GM-CSF, TNFa, resting	18.17
monocytes, LPS, gIFN, anti-IL-10	18.27
DC ex monocytes GM-CSF, IL-4, LPS activated 4+16 hr	18.51
DC ex monocytes GM-CSF, IL-4, monokine activated 4+16 hr	18.68
kidney epithelial carcinoma cell line CHA, activated	18.69
monocytes, LPS, 1 hr	18.72
monocytes, LPS, 6 hr	18.72
DC 70% CD1a+, ex CD34+ GM-CSF, TNFa, activated 1 hr	18.91
DC 70% CD1a+, ex CD34+ GM-CSF, TNFa, activated 6 hr	18.94
T cell, TH1 clone HY06, activated	18.99
lung fetal	19.15
T cell, TH1 clone HY06, resting	19.18
T cell, TH1 clone HY06, anergic	19.23
monocytes, LPS, gIFN, IL-10, 4+16 hr	19.3
spleen fetal	19.51
testes fetal	19.7
T cell, TH0 clone Mot 72, resting	19.71
T cell, TH0 clone Mot 72, resting	19.84
DC CD1a+ CD86+, ex CD34+ GM-CSF, TNFa, activated 1+6 hr	19.94
peripheral blood mononuclear cells, activated	20.01
hematopoietic precursor line TF1, activated	20.07
lung fibroblast sarcoma line MRC5, activated	20.18
Splenocytes, activated	20.21
T cell gd clones, resting	20.27
ovary fetal	20.45
T cells CD4+, TH2 polarized, activated	20.57
Splenocytes, resting	20.6
uterus fetal	20.62
DC 95% CD1a+, ex CD34+ GM-CSF, TNFa, activated 1+6 hr	20.94
epithelial cells, unstimulated	20.96
peripheral blood mononuclear cells, resting	20.97
adipose tissue fetal	21.13

B cell line JY, activated	21.28
monocytes, LPS, gIFN, IL-10	21.37
placenta 28 wk	21.38
NK 20 clones pooled, activated	21.55
pool of two normal human lung samples	21.63
normal human thyroid	21.65
epithelial cells, IL-1b activated	21.72
normal human skin	21.84
T cell, TH0 clone Mot 72, anergic	21.87
small intestine fetal	22.01
CD28- T cell clone in pME	22.08
T cell, TH2 clone HY935, activated	22.09
T cell clones, pooled, resting	22.29
Hashimoto's thyroiditis thyroid sample	22.3
NK 20 clones pooled, resting	22.4
B cell EBV lines, resting	22.45
T cell, TH2 clone HY935, resting	22.86
T cell, TH0 clone Mot 72, activated	23.3
monocytes, LPS, gIFN, anti-IL-10, 4+16 hr	23.39
T cell lines Jurkat and Hut78, resting	23.4
T cell, TH0 clone Mot 72, activated	23.56
Pneumocystic carnii pneumonia lung sample	24.05
U937 premonocytic line, resting	25.01
pool of rheumatoid arthritis samples, human	25.85
pool of three heavy smoker human lung samples	26.1
DC 95% CD14+, ex CD34+ GM-CSF, TNFa, activated 1+6 hr	32.69
kidney fetal	33.7
liver fetal	34.4
NK cytotoxic clone, resting	34.49
tonsil inflammed	35.02
normal w.t. monkey lung	35.45
gallbladder fetal	35.84
TR1 T cell clone	35.86
allergic lung sample	36.39
Psoriasis patient skin sample	36.44
normal human colon	37.34
brain fetal	37.35
Ascaris-challenged monkey lung, 4 hr.	37.75
Ascaris-challenged monkey lung, 24 hr.	40
heart fetal	40
normal w.t. monkey colon	40
ulcerative colitis human colon sample	40

Primers specific for DCRS6_H were designed and used in Taqman quantative PCR against various human libraries. DCRS6_H is expressed in innate immune myeloid cells including dendritic cells and monocytes. Expression is also detected in T-cell libraries. These data demonstrate the receptor is expressed in immune cell types and may be regulated by activation conditions.

Table for DCRS6_H

library description	CT for DCRS6_H
T cell, TH0 clone Mot 72, resting	15.54
T cell, TH0 clone Mot 72, resting	15.7
DC ex monocytes GM-CSF, IL-4, resting	17.84
DC ex monocytes GM-CSF, IL-4, resting	18.19
DC ex monocytes GM-CSF, IL-4, LPS activated 4+16 hr	18.3
DC ex monocytes GM-CSF, IL-4, monokine activated 4+16 hr	18.3
T cell, TH1 clone HY06, resting	18.43
NK cytotoxic clone, resting	18.53
T cell clones, pooled, resting	18.8
T cell, TH1 clone HY06, activated	19.03
T cell, TH2 clone HY935, activated	19.1
TR1 T cell clone	19.12
T cells CD4+, TH2 polarized, activated	20.06
B cell EBV lines, resting	20.3
T cell, TH2 clone HY935, resting	20.48
kidney epithelial carcinoma cell line CHA, activated	21.07
T cell, TH1 clone HY06, anergic	21.14
normal human colon	21.29
NK 20 clones pooled, resting	21.49
T cell gd clones, resting	21.58
gallbladder fetal	22.21
kidney fetal	22.79
liver fetal	22.8
Pneumocystic carnii pneumonia lung sample	23.06
CD28- T cell clone in pME	23.18
T cell, TH0 clone Mot 72, anergic	23.2
ovary fetal	23.51
normal human thyroid	24.03
small intestine fetal	24.13
testes fetal	24.82
epithelial cells, IL-1b activated	26.08
pool of three heavy smoker human lung samples	26.49
placenta 28 wk	26.56
normal w.t. monkey lung	28.65
peripheral blood mononuclear cells,	33.39

activated	
Ascaris-challenged monkey lung, 4 hr.	36.59
spleen fetal	38.43
peripheral blood mononuclear cells, resting	40
T cell, TH0 clone Mot 72, activated	40
T cell lines Jurkat and Hut78, resting	40
Splenocytes, resting	40
Splenocytes, activated	40
B cell line JY, activated	40
NK 20 clones pooled, activated	40
hematopoietic precursor line TF1, activated	40
U937 premonocytic line, resting	40
U937 premonocytic line, activated	40
monocytes, LPS, gIFN, anti-IL-10	40
monocytes, LPS, gIFN, IL-10	40
monocytes, LPS, gIFN, anti-IL-10, 4+16 hr	40
monocytes, LPS, gIFN, IL-10, 4+16 hr	40
monocytes, LPS, 1 hr	40
monocytes, LPS, 6 hr	40
DC 70% CD1a+, ex CD34+ GM-CSF, TNFa, resting	40
DC 70% CD1a+, ex CD34+ GM-CSF, TNFa, activated 1 hr	40
DC 70% CD1a+, ex CD34+ GM-CSF, TNFa, activated 6 hr	40
DC 95% CD1a+, ex CD34+ GM-CSF, TNFa, activated 1+6 hr	40
DC 95% CD14+, ex CD34+ GM-CSF, TNFa, activated 1+6 hr	40
DC CD1a+ CD86+, ex CD34+ GM-CSF, TNFa, activated 1+6 hr	40
epithelial cells, unstimulated	40
lung fibroblast sarcoma line MRC5, activated	40
Ascaris-challenged monkey lung, 24 hr.	40
pool of two normal human lung samples	40
allergic lung sample	40
normal w.t. monkey colon	40
ulcerative colitis human colon sample	40
Hashimoto's thyroiditis thyroid sample	40
pool of rheumatoid arthritis samples, human	40
normal human skin	40
Psoriasis patient skin sample	40
tonsil inflammed	40
lung fetal	40
heart fetal	40
brain fetal	40
adipose tissue fetal	40
uterus fetal	40

T cell, TH0 clone Mot 72, activated	40

Primers specific for DCRS7_H were designed and used in Taqman quantative PCR against various human libraries. DCRS7_H is expressed in innate immune myeloid cells including dendritic cells and monocytes. Expression is also detected in fetal libraries. These data demonstrate the receptor is expressed in immune cell types and may be regulated by activation conditions.

Table for DCRS7_H

library description	**CT for DCRS7_H**
fetal uterus	19.05
DC mix	19.34
fetal small intestine	19.46
fetal ovary	19.68
fetal testes	19.75
fetal lung	20.04
CHA	20.24
normal thyroid	20.32
DC/GM/IL-4	20.52
fetal spleen	20.86
normal lung	20.94
TF1	21
allergic lung #19	21.02
Psoriasis skin	21.07
fetal liver	21.15
MRC5	21.15
24 hr. Ascaris lung	21.17
hi dose IL-4 lung	21.23
CD1a+ 95%	21.32
Hashimotos thyroiditis	21.35
Crohns colon 4003197A	21.35
normal lung pool	21.36
70% DC resting	21.42
fetal kidney	21.58
adult placenta	21.68
lung 121897-1	21.8
Pneumocystis carnii lung #20	21.81
A549 unstim.	21.89
normal colon #22	21.94
18 hr. Ascaris lung	22.09
normal skin	22.1
Crohns colon 9609C144	22.13
fetal adipose tissue	22.35
D6	22.39

DC resting CD34-derived	22.45
DC TNF/TGFb act CD34-der.	22.54
fetal brain	22.9
DC CD40L activ. mono-deriv.	22.91
Crohns colon 403242A	22.91
ulcerative colitis colon #26	23
RA synovium pool	23.06
A549 activated	23.06
mono + IL-10	23.42
DC LPS	23.49
Mot 72 activated	23.66
CD1a+ CD86+	23.86
HY06 resting	23.87
U937 activated	23.97
inflammed tonsil	23.97
D1	24.06
M1	24.17
CD14+ 95%	24.21
lung 080698-2	24.28
4 hr. Ascaris lung	24.37
Jurkat activated pSPORT	24.42
DC resting mono-derived	24.48
HY06 activated	24.54
C+	24.64
Splenocytes resting	24.65
U937/CD004 resting	24.96
PBMC resting	25.8
Mot 72 resting	25.91
mono + anti-IL-10	26.14
NK pool	26.99
HY06 anti-peptide	27.34
mast cell pME	27.38
Tc gamma delta	28.14
TC1080 CD28- pMET7	31.05
PBMC activated	31.89
NK non cytotox.	32.3
RV-C30 TR1 pMET7	32.5
Bc	33.72
C-	33.8
Splenocytes activated	34.7
JY	35.05
NK cytotox.	36.44
NKL/IL-2	37.59
HY935 resting	37.6
NK pool activated	38.15
Mot 72 anti-peptide	38.87
fetal heart	40.92

B21 resting	42.05
Jurkat resting pSPORT	42.8
B21 activated	43.09
NKA6 pSPORT	44.85
HY935 activated	45
M6	45

Primers specific for DCRS9_H were designed and used in Taqman quantative PCR against various human libraries. DCRS9_H is expressed T-cells, fetal lung, and resting monocytes. These data demonstrate the receptor is expressed in immune cell types and may be regulated by activation conditions.

Table for DCRS9_H

library description	**CT for DCRS9_H**
HY06 resting	22.35
fetal lung	22.63
HY06 anti-peptide	22.72
HY06 activated	22.96
U937/CD004 resting	24.16
fetal small intestine	24.94
JY	25.04
Mot 72 resting	25.12
Jurkat activated pSPORT	25.2
RV-C30 TR1 pMET7	26.51
fetal kidney	26.76
MRC5	27.2
Psoriasis skin	27.3
Tc gamma delta	27.37
Crohns colon 4003197A	27.44
fetal spleen	27.72
normal lung	27.83
Hashimotos thyroiditis	28.03
B21 resting	28.32
TF1	28.39
NK cytotox.	28.44
TC1080 CD28- pMET7	28.61
Pneumocystis carnii lung #20	29.05
U937 activated	29.06
HY935 resting	29.09
CD1a+ 95%	29.13

B21 activated	29.2
Mot 72 activated	29.21
fetal testes	29.27
lung 080698-2	29.32
Jurkat resting pSPORT	29.38
CD14+ 95%	29.38
normal thyroid	29.53
Mot 72 anti-peptide	29.65
Splenocytes resting	29.85
Crohns colon 9609C144	30.28
lung 121897-1	30.37
24 hr. Ascaris lung	30.59
hi dose IL-4 lung	30.8
CD1a+ CD86+	31.42
normal skin	31.73
fetal uterus	31.79
PBMC activated	31.82
inflammed tonsil	31.98
fetal brain	32.21
RA synovium pool	32.77
allergic lung #19	33.18
18 hr. Ascaris lung	33.42
adult placenta	33.43
normal lung pool	33.45
Crohns colon 403242A	33.52
NK pool	33.72
HY935 activated	33.75
DC/GM/IL-4	34.28
DC resting mono-derived	34.57
fetal ovary	35.06
fetal adipose tissue	35.07
CHA	35.2
PBMC resting	35.95
Bc	36.19
A549 unstim.	36.4
fetal heart	36.87
ulcerative colitis colon #26	37.83
C-	38.32
4 hr. Ascaris lung	40.2
D6	40.62
C+	44.38

A549 activated	44.58
Splenocytes activated	45
NK pool activated	45
NKA6 pSPORT	45
NKL/IL-2	45
NK non cytotox.	45
mono + anti-IL-10	45
mono + IL-10	45
M1	45
M6	45
70% DC resting	45
D1	45
DC LPS	45
DC mix	45
fetal liver	45
mast cell pME	45
DC CD40L activ. mono-deriv.	45
DC resting CD34-derived	45
DC TNF/TGFb act CD34-der.	45
normal colon #22	45

V. Cloning of species counterparts

Various strategies are used to obtain species counterparts of the DCRSs, preferably from other primates or rodents. One method is by cross hybridization using closely related species DNA probes. It may be useful to go into evolutionarily similar species as intermediate steps. Another method is by using specific PCR primers based on the identification of blocks of similarity or difference between genes, e.g., areas of highly conserved or nonconserved polypeptide or nucleotide sequence. Sequence database searches may identify species counterparts.

VI. Production of mammalian protein

An appropriate, e.g., GST, fusion construct is engineered for expression, e.g., in E. coli. For example, a mouse IGIF pGex plasmid is constructed and transformed into E. coli. Freshly transformed cells are grown, e.g., in LB medium containing 50 μg/ml ampicillin and induced with IPTG (Sigma, St. Louis, MO). After overnight induction, the bacteria are harvested and the pellets containing the appropriate protein are isolated. The pellets are homogenized, e.g., in TE buffer (50 mM Tris-base pH 8.0, 10 mM EDTA and 2 mM pefabloc) in 2 liters. This material is passed through a microfluidizer (Microfluidics, Newton, MA) three times. The fluidized supernatant is spun down on a Sorvall GS-3 rotor for 1 h at 13,000 rpm. The resulting supernatant containing the cytokine receptor protein is filtered and passed over a glutathione-SEPHAROSE column equilibrated in 50 mM Tris-base pH 8.0. Fractions containing the DCRS8-GST fusion protein are pooled and cleaved, e.g., with thrombin (Enzyme Research Laboratories, Inc., South Bend, IN). The cleaved pool is then passed over a Q-SEPHAROSE column equilibrated in 50 mM Tris-base. Fractions containing DCRS8 are pooled and diluted in cold distilled H_2O, to lower the conductivity, and passed back over a fresh Q-Sepharose column, alone or in succession with an immunoaffinity antibody column. Fractions containing the DCRS8 protein are pooled, aliquoted, and stored in the -70° C freezer.

Comparison of the CD spectrum with cytokine receptor protein may suggest that the protein is correctly folded. See Hazuda, et al. (1969) J. Biol. Chem. 264:1689-1693.

VII. Preparation of specific antibodies

Inbred Balb/c mice are immunized intraperitoneally with recombinant forms of the protein, e.g., purified DCRS8 or stable transfected NIH-3T3 cells. Animals are boosted at appropriate time points with protein, with or without additional adjuvant, to further stimulate antibody production. Serum is collected, or hybridomas produced with harvested spleens.

Alternatively, Balb/c mice are immunized with cells transformed with the gene or fragments thereof, either endogenous or exogenous cells, or with isolated membranes enriched for expression of the antigen. Serum is collected at the appropriate time, typically after numerous further administrations. Various gene therapy techniques may be useful, e.g., in producing protein in situ, for generating an immune response. Serum or antibody preparations may be cross-absorbed or immunoselected to prepare substantially purified antibodies of defined specificity and high affinity.

Monoclonal antibodies may be made. For example, splenocytes are fused with an appropriate fusion partner and hybridomas are selected in growth medium by standard procedures. Hybridoma supernatants are screened for the presence of antibodies which bind to the DCRS8, e.g., by ELISA or other assay. Antibodies which specifically recognize specific DCRS8 embodiments may also be selected or prepared.

In another method, synthetic peptides or purified protein are presented to an immune system to generate monoclonal or polyclonal antibodies. See, e.g., Coligan (ed. 1991) Current Protocols in Immunology Wiley/Greene; and Harlow and Lane (1989) Antibodies: A Laboratory Manual Cold Spring Harbor Press. In appropriate situations, the binding reagent is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to a substrate for panning methods. Nucleic acids may also be introduced into cells in an animal to produce the antigen, which serves to elicit an immune response. See, e.g., Wang, et al. (1993) Proc. Nat'l. Acad. Sci. 90:4156-4160; Barry, et al. (1994) BioTechniques 16:616-619; and Xiang, et al. (1995) Immunity 2: 129-135.

VIII. Production of fusion proteins

Various fusion constructs are made with DCRS8 or DCRS9. A portion of the appropriate gene is fused to an epitope tag, e.g., a FLAG tag, or to a two hybrid system construct. See, e.g., Fields and Song (1989) Nature 340:245-246.

The epitope tag may be used in an expression cloning procedure with detection with anti-FLAG antibodies to detect a binding partner, e.g., ligand for the respective cytokine receptor. The two hybrid system may also be used to isolate proteins which specifically bind to the receptor subunit.

IX. Structure activity relationship

Information on the criticality of particular residues is determined using standard procedures and analysis. Standard mutagenesis analysis is performed, e.g., by generating many different variants at determined positions, e.g., at the positions identified above, and evaluating biological activities of the variants. This may be performed to the extent of determining positions which modify activity, or to focus on specific positions to

determine the residues which can be substituted to either retain, block, or modulate biological activity.

Alternatively, analysis of natural variants can indicate what positions tolerate natural mutations. This may result from populational analysis of variation among individuals, or across strains or species. Samples from selected individuals are analyzed, e.g., by PCR analysis and sequencing. This allows evaluation of population polymorphisms.

X. Isolation of a ligand

A cytokine receptor can be used as a specific binding reagent to identify its binding partner, by taking advantage of its specificity of binding, much like an antibody would be used. The binding receptor may be a heterodimer of receptor subunits; or may involve, e.g., a complex of the DCRS8 with another cytokine receptor subunit. A binding reagent is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to a substrate for panning methods.

The binding composition is used to screen an expression library made from a cell line which expresses a binding partner, i.e., ligand, preferably membrane associated. Standard staining techniques are used to detect or sort surface expressed ligand, or surface expressing transformed cells are screened by panning. Screening of intracellular expression is performed by various staining or immunofluorescence procedures. See also McMahan, et al. (1991) EMBO J. 10:2821-2832.

For example, on day 0, precoat 2-chamber permanox slides with 1 ml per chamber of fibronectin, 10 ng/ml in PBS, for 30 min at room temperature. Rinse once with PBS. Then plate COS cells at 2-3 x 10^5 cells per chamber in 1.5 ml of growth media. Incubate overnight at 37 C.

On day 1 for each sample, prepare 0.5 ml of a solution of 66 µg/ml DEAE-dextran, 66 µM chloroquine, and 4 µg DNA in serum free DME. For each set, a positive control is prepared, e.g., of DCRS8-FLAG cDNA at 1 and 1/200 dilution, and a negative mock. Rinse cells with serum free DME. Add the DNA solution and incubate 5 hr at 37 C. Remove the medium and add 0.5 ml 10% DMSO in DME for 2.5 min. Remove and wash once with DME. Add 1.5 ml growth medium and incubate overnight.

On day 2, change the medium. On days 3 or 4, the cells are fixed and stained. Rinse the cells twice with Hank's Buffered Saline Solution (HBSS) and fix in 4% paraformaldehyde (PFA)/glucose for 5 min. Wash 3X with HBSS. The slides may be stored at -80 C after all liquid is removed. For each chamber, 0.5 ml incubations are performed as follows. Add HBSS/saponin (0.1%) with 32 µl/ml of 1 M NaN_3 for 20 min. Cells are then washed with HBSS/saponin 1X. Add appropriate DCRS8 or

DCRS8/antibody complex to cells and incubate for 30 min. Wash cells twice with HBSS/saponin. If appropriate, add first antibody for 30 min. Add second antibody, e.g., Vector anti-mouse antibody, at 1/200 dilution, and incubate for 30 min. Prepare ELISA solution, e.g., Vector Elite ABC horseradish peroxidase solution, and preincubate for 30 min. Use, e.g., 1 drop of solution A (avidin) and 1 drop solution B (biotin) per 2.5 ml HBSS/saponin. Wash cells twice with HBSS/saponin. Add ABC HRP solution and incubate for 30 min. Wash cells twice with HBSS, second wash for 2 min, which closes cells. Then add Vector diaminobenzoic acid (DAB) for 5 to 10 min. Use 2 drops of buffer plus 4 drops DAB plus 2 drops of H_2O_2 per 5 ml of glass distilled water. Carefully remove chamber and rinse slide in water. Air dry for a few minutes, then add 1 drop of Crystal Mount and a cover slip. Bake for 5 min at 85-90 C.

Evaluate positive staining of pools and progressively subclone to isolation of single genes responsible for the binding.

Alternatively, receptor reagents are used to affinity purify or sort out cells expressing a putative ligand. See, e.g., Sambrook, et al. or Ausubel, et al.

Another strategy is to screen for a membrane bound receptor by panning. The receptor cDNA is constructed as described above. Immobilization may be achieved by use of appropriate antibodies which recognize, e.g., a FLAG sequence of a DCRS8 fusion construct, or by use of antibodies raised against the first antibodies. Recursive cycles of selection and amplification lead to enrichment of appropriate clones and eventual isolation of receptor expressing clones.

Phage expression libraries can be screened by mammalian DCRS8. Appropriate label techniques, e.g., anti-FLAG antibodies, will allow specific labeling of appropriate clones.

We tested the ability of DCRS receptors to specifically bind IL-17 family cytokines. Recombinant FLAG-hIL-17 family cytokines were used in binding experiments on Baf/3 DCRS receptor transfected expressing recombinant IL-17R_H, DCRS6_H, DCRS7_H, DCRS8_H and DCRS9_H and analyzed by FACS. We can demonstrate specific binding of IL-17 family member IL-74 to DCRS6 expressing Baf/3 cells. In additional experiments we have shown IL-17 specific binding to IL-17R_H, DCRS7_H, DCRS8_H. Further experiments show IL-71 binding to DCRS8_Hu transfectants. These experiments demonstrate the sequence homology among IL-17 related cytokine receptors confers functional binding to IL-17 cytokines.

All citations herein are incorporated herein by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled; and the invention is not to be limited by the specific embodiments that have been presented herein by way of example.

WHAT IS CLAIMED IS:

1. A composition of matter selected from:

a) a substantially pure or recombinant polypeptide comprising at least three distinct nonoverlapping segments of at least four amino acids identical to segments of SEQ ID NO: 14;

b) a substantially pure or recombinant polypeptide comprising at least two distinct nonoverlapping segments of at least five amino acids identical to segments of SEQ ID NO: 14;

c) a natural sequence DCRS8 comprising mature SEQ ID NO: 14;

d) a fusion polypeptide comprising DCRS8 sequence;

e) a substantially pure or recombinant polypeptide comprising at least three distinct nonoverlapping segments of at least four amino acids identical to segments of SEQ ID NO: 17 or 20;

f) a substantially pure or recombinant polypeptide comprising at least two distinct nonoverlapping segments of at least five amino acids identical to segments of SEQ ID NO: 17 or 20;

g) a natural sequence DCRS9 comprising mature SEQ ID NO: 17 or 20; or

h) a fusion polypeptide comprising DCRS9 sequence.

2. The substantially pure or isolated antigenic polypeptide of Claim 1, wherein said distinct nonoverlapping segments of identity include:

a) one of at least eight amino acids;

b) one of at least four amino acids and a second of at least five amino acids;

c) at least three segments of at least four, five, and six amino acids, or

d) one of at least twelve amino acids.

3. The composition of matter of Claim 1, wherein said:

a) polypeptide:

i) comprises a mature sequence of Table 3 or 4;

ii) is an unglycosylated form of DCRS8 or DCRS9;

iii) is from a primate, such as a human;

iv) comprises at least seventeen amino acids of SEQ ID NO: 14 or 17;

v) exhibits at least four nonoverlapping segments of at least seven amino acids of SEQ ID NO: 14 or 17;

vi) is a natural allelic variant of DCRS8 or DCRS9;

vii) has a length at least about 30 amino acids;

viii) exhibits at least two non-overlapping epitopes which are specific for a primate DCRS8 or DCRS9;
ix) is glycosylated;
x) has a molecular weight of at least 30 kD with natural glycosylation;
xi) is a synthetic polypeptide;
xii) is attached to a solid substrate;
xiii) is conjugated to another chemical moiety;
xiv) is a 5-fold or less substitution from natural sequence; or
xv) is a deletion or insertion variant from a natural sequence.

4. A composition comprising:
a) a substantially pure DCRS8 or DCRS9 and another cytokine receptor family member;
b) a sterile DCRS8 or DCRS9 polypeptide of Claim 1;
c) said DCRS8 or DCRS9 polypeptide of Claim 1 and a carrier, wherein said carrier is:
i) an aqueous compound, including water, saline, and/or buffer; and/or
ii) formulated for oral, rectal, nasal, topical, or parenteral administration.

5. The fusion polypeptide of Claim 1, comprising:
a) mature protein sequence of Table 3 or 4;
b) a detection or purification tag, including a FLAG, His6, or Ig sequence; or
c) sequence of another cytokine receptor protein.

6. A kit comprising a polypeptide of Claim 1, and:
a) a compartment comprising said protein or polypeptide; or
b) instructions for use or disposal of reagents in said kit.

7. A binding compound comprising an antigen binding site from an antibody, which specifically binds to a natural DCRS8 or DCRS9 polypeptide of Claim 1, wherein:
a) said binding compound is in a container;
b) said DCRS8 or DCRS9 polypeptide is from a human;
c) said binding compound is an Fv, Fab, or Fab2 fragment;
d) said binding compound is conjugated to another chemical moiety; or
e) said antibody:
i) is raised against a peptide sequence of a mature polypeptide of Table 3 or 4;

ii) is raised against a mature DCRS8 or DCRS9;
iii) is raised to a purified human DCRS8 or DCRS9;
iv) is immunoselected;
v) is a polyclonal antibody;
vi) binds to a denatured DCRS8 or DCRS9;
vii) exhibits a Kd to antigen of at least 30 μM;
viii) is attached to a solid substrate, including a bead or plastic membrane;
ix) is in a sterile composition; or
x) is detectably labeled, including a radioactive or fluorescent label.

8. A kit comprising said binding compound of Claim 7, and:
a) a compartment comprising said binding compound; or
b) instructions for use or disposal of reagents in said kit.

9. A method of producing an antigen:antibody complex, comprising contacting under appropriate conditions a primate DCRS8 or DCRS9 polypeptide with an antibody of Claim 7, thereby allowing said complex to form.

10. The method of Claim 9, wherein:
a) said complex is purified from other cytokine receptors;
b) said complex is purified from other antibody;
c) said contacting is with a sample comprising an interferon;
d) said contacting allows quantitative detection of said antigen;
e) said contacting is with a sample comprising said antibody; or
f) said contacting allows quantitative detection of said antibody.

11. A composition comprising:
a) a sterile binding compound of Claim 7, or
b) said binding compound of Claim 7 and a carrier, wherein said carrier is:
i) an aqueous compound, including water, saline, and/or buffer; and/or
ii) formulated for oral, rectal, nasal, topical, or parenteral administration.

12. An isolated or recombinant nucleic acid encoding said polypeptide of Claim 1, wherein said:
a) DCRS8 or DCRS9 is from a human; or
b) said nucleic acid:
i) encodes an antigenic peptide sequence of Table 3 or 4;

ii) encodes a plurality of antigenic peptide sequences of Table 3 or 4;
iii) exhibits identity over at least thirteen nucleotides to a natural cDNA encoding said segment;
iv) is an expression vector;
v) further comprises an origin of replication;
vi) is from a natural source;
vii) comprises a detectable label;
viii) comprises synthetic nucleotide sequence;
ix) is less than 6 kb, preferably less than 3 kb;
x) is from a primate;
xi) comprises a natural full length coding sequence;
xii) is a hybridization probe for a gene encoding said DCRS8 or DCRS9; or
xiii) is a PCR primer, PCR product, or mutagenesis primer.

13. A cell or tissue comprising said recombinant nucleic acid of Claim 12.

14. The cell of Claim 13, wherein said cell is:
a) a prokaryotic cell;
b) a eukaryotic cell;
c) a bacterial cell;
d) a yeast cell;
e) an insect cell;
f) a mammalian cell;
g) a mouse cell;
h) a primate cell; or
i) a human cell.

15. A kit comprising said nucleic acid of Claim 12, and:
a) a compartment comprising said nucleic acid;
b) a compartment further comprising a primate DCRS8 or DCRS9 polypeptide; or
c) instructions for use or disposal of reagents in said kit.

16. A nucleic acid which:
a) hybridizes under wash conditions of 30 minutes at 30° C and less than 2M salt to the coding portion of SEQ ID NO: 13 or 16; or

b) exhibits identity over a stretch of at least about 30 nucleotides to a primate DCRS8 or DCRS9.

17. The nucleic acid of Claim 16, wherein:

a) said wash conditions are at 45° C and/or 500 mM salt; or

b) said stretch is at least 55 nucleotides.

18. The nucleic acid of Claim 16, wherein:

a) said wash conditions are at 55° C and/or 150 mM salt; or

b) said stretch is at least 75 nucleotides.

19. A method of modulating physiology or development of a cell or tissue culture cells comprising contacting said cell with an agonist or antagonist of a mammalian DCRS8 or DCRS9.

20. The method of Claim 19, wherein said cell is transformed with a nucleic acid encoding said DCRS8 or DCRS9 and another cytokine receptor subunit.

```
DCRS7_Mu      RTALLLHSADG-AGYERLVGALASALSQMP---LRVAVDLWSRRE-LSAHGALAWFHHQR
DCRS7_Hu      RAALLLYSADD-SGFERLVGALASALCQLP---LRVAVDLWSRRE-LSAQGPVAWFHAQR
IL-17R_Hu     RKVWIIYSADH-PLYVDVVLKFAQFLLTACG--TEVALDLLEEQA-ISEAGVMTWVGRQK
IL-17R_Mu     RKVWIVYSADH-PLYVEVVLKFAQFLITACG--TEVALDLLEEQV-ISEVGVMTWVSRQK
DCRS10        RKVFITYSMD----TAMEVVKFVNFLLVNG---FQTAIDIFEDR--IRGIDIIKWMERYL
DCRS10_Mu     RKVFITYSMD----TAMEVVKFVNFLLVNG---FQTAIDIFEDR--IRGIDIIKWMERYL
DCRS9_Hu      RPVLLLHAADS-EAQRRLVGALAELLRAALGGGRDVIVDLWEGRH-VARVGPLPWLWAAR
DCRS8_Hu      PKVFLCYSSKDGQNHMNVVQCFAYFLQDFCG--CEVALDLWEDFS-LCREGQREWVIQKI
IL-17R_Ce     VKVMIVYADDN-DLHTDCVKKLVENLRNCAS--CDPVFDLEKLI--TAEIVPSRWLVDQI
DCRS6_Hu      IKVLVVYPSEI--CFHHTICYFTEFLQNHCR--SEVILEKWQKKK-IAEMGPVQWLATQK
DCRS6_Ce      FKVMLVCPEVS-GRDEDFMMRIADALKKSN---NKVVCDRWFEDSKNAEENMLHWVYEQT
                . :  .          :  :.  *            :               *.

DCRS7_Mu      RRILQEGGVVILLFSPAAVAQCQ---QWLQLQTVEP---GP---HDALAAWLSCVLPDFL
DCRS7_Hu      RQTLQEGGVVVLLFSPGAVALCS---EWLQDGVSGPGAHGP---HDAFRASLSCVLPDFL
IL-17R_Hu     QEMVESNSKIIVLCSRGTRAKWQALLGRGAP-VRLRCDHGKPV-GDLFTAAMNMILPDFK
IL-17R_Mu     QEMVESNSKIIILCSRGTQAKWKAILGWAEPAVQLRCDHWKPA-GDLFTAAMNMILPDFK
DCRS10        R---DKTVMIIVAISPKYKQDVE----GAESQLDED-EHGL---HTKYIHRM-MQIEFIK
DCRS10_Mu     R---DKTVMIIVAISPKYKQDVE----GAESQLDED-EHGL---HTKYIHRM-MQIEFIS
DCRS9_Hu      TRVAREQGTVLLLWSGADLRPVS----GPDP-RAAP-----------LLA----LLHAAP
DCRS8_Hu      H----ESQFIIVVCSKGMKYFVD---KKNYKHKGGGRGSGK---GELFLVAVSAIAEKLR
IL-17R_Ce     S----SLKKFIIVVSDCAEKILD----TEASETHQLVQARP--FADLFGPAMEMIIRDAT
DCRS6_Hu      K----AADKVVFLLSNDVNSVCD----GTCGKSEGSPSENS---QDLFPLAFNLFCSDLR
DCRS6_Ce      K----IAEKIIVFHSAYYHPRCG---IYDVINNFFPCTDPR-----LAHIALT---PEAQ
                       .:.  *
```

FIG. 1A

```
DCRS7_Mu     QGRATGR-----YVGVYFDGLLHPDSVPSPFRVAPLFSLP-SQLPAFLDALQ--GGCSTS
DCRS7_Hu     QGRAPGS-----YVGACFDRLLHPDAVPALFRTVPVFTLP-SQLPDFLGALQ--QPRAPR
IL-17R_Hu    RPACFGT-----YVVCYFSEVSCDGDVPDLFGAAPRYPLM-DRFEEVYFRIQ--DLEMFQ
IL-17R_Mu    RPACFGT-----YVVCYFSGICSERDVPDLFNITSRYPLM-DRFEEVYFRIQ--DLEMFE
DCRS10       QGSMNFR-----FIPVLFPNAK-KEHVPTWLQNTHVYSWP-KNKKNILLRLL-REEEYVA
DCRS10_Mu    QGSMNFR-----FIPVLFPNAK-KEHVPTWLQNTHVYSWP-KNKKNILLRLL-REEEYVA
DCRS9_Hu     RPL---------LLLAYFSRLCAKGDIPPPLRALPRYRLL-RDLPRLLRALD--ARPFAE
DCRS8_Hu     QAKQSSSAALSKFIAVYFDYSC-EGDVPGILDLSTKYRLM-DNLPQLCSHLHSRDHGLQE
IL-17R_Ce    HNFPEAR---KKYAVVRFNYSP---HVPPNLAILNLPTFIPEQFAQLTAFLHN-VEHTER
DCRS6_Hu     SQIHLHK-----YVVVYFREID-TKDDYNALSVCPKYHLM-KDATAFCAELL---HVKQQ
DCRS6_Ce     RSVPKEV----EYVLPRDQKLL--EDAFDITIADPLVIDIPIEDVAIPENVP--IHHESC
                                                          .     :

DCRS7_Mu     AGRPADRVER-----VT----QALRSALDSCTS-----------
DCRS7_Hu     SGRLQERAEQ-----VS----RALQPALDSYFHPP---------
IL-17R_Hu    PGRMHRVGELSGDNYLRS---PGGRQLRAALDRFRDWQVRCPDW
IL-17R_Mu    PGRMHHVRELTGDNYLQS---PSGRQLKEAVLRFQEWQTQCPDW
DCRS10       P----PRGPL-----------PTLQVVPL---------------
DCRS10_Mu    P----PRGPL-----------PTLQVVPL---------------
DCRS9_Hu     ATSWGRLGAR-----------QRRQSRLELCSR-----------
DCRS8_Hu     PGQHTRQGSR-----RNYFRSKSGRSLYVAICNMHQFIDEEPDW
IL-17R_Ce    ANVTQNISEA------Q------IHEWNLCASRMMSFFVRNPNW
DCRS6_Hu     VS----AGKR-------------SQACHDGCCSL----------
DCRS6_Ce     DSIDSRNNSK-------------THSTDSGVSSLSS----NS--
                                     :
```

FIG. 1B

SEQUENCE SUBMISSION

SEQ ID NO: 1 is primate DCRS6 nucleotide sequence.
SEQ ID NO: 2 is primate DCRS6 polypeptide sequence.
SEQ ID NO: 3 is primate DCRS6 reverse translation.
SEQ ID NO: 4 is rodent DCRS6 nucleotide sequence.
SEQ ID NO: 5 is rodent DCRS6 polypeptide sequence.
SEQ ID NO: 6 is rodent DCRS6 reverse translation.
SEQ ID NO: 7 is primate DCRS7 nucleotide sequence.
SEQ ID NO: 8 is primate DCRS7 polypeptide sequence.
SEQ ID NO: 9 is primate DCRS7 reverse translation.
SEQ ID NO: 10 is rodent DCRS7 nucleotide sequence.
SEQ ID NO: 11 is rodent DCRS7 polypeptide sequence.
SEQ ID NO: 12 is rodent DCRS7 reverse translation.
SEQ ID NO: 13 is primate DCRS8 nucleotide sequence.
SEQ ID NO: 14 is primate DCRS8 polypeptide sequence.
SEQ ID NO: 15 is primate DCRS8 reverse translation.
SEQ ID NO: 16 is primate DCRS9 nucleotide sequence.
SEQ ID NO: 17 is primate DCRS9 polypeptide sequence.
SEQ ID NO: 18 is primate DCRS9 reverse translation.
SEQ ID NO: 19 is rodent DCRS9 nucleotide sequence.
SEQ ID NO: 20 is rodent DCRS9 polypeptide sequence.
SEQ ID NO: 21 is rodent DCRS9 reverse translation.
SEQ ID NO: 22 is primate DCRS10 nucleotide sequence.
SEQ ID NO: 23 is primate DCRS10 polypeptide sequence.
SEQ ID NO: 24 is primate DCRS10 reverse translation.
SEQ ID NO: 25 is rodent DCRS10 nucleotide sequence.
SEQ ID NO: 26 is rodent DCRS10 polypeptide sequence.
SEQ ID NO: 27 is rodent DCRS10 reverse translation.
SEQ ID NO: 28 is primate IL-17 receptor peptide sequence.
SEQ ID NO: 29 is rodent IL-17 receptor peptide sequence.
SEQ ID NO: 30 is worm IL-17 receptor peptide sequence.
SEQ ID NO: 31 is worm DCRS6 nucleotide sequence.

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<120> Mammalian Receptor Proteins; Related Reagents and
Methods

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Homo sapiens

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                -10                 -5                  -1   1

gta ccc cga gag ccg acc gtt caa tgt ggc tct gaa act ggg cca tct      96
Val Pro Arg Glu Pro Thr Val Gln Cys Gly Ser Glu Thr Gly Pro Ser
            5                  10                  15

cca gag tgg atg cta caa cat gat cta atc ccg gga gac ttg agg gac     144
Pro Glu Trp Met Leu Gln His Asp Leu Ile Pro Gly Asp Leu Arg Asp
        20                  25                  30

ctc cga gta gaa cct gtt aca act agt gtt gca aca ggg gac tat tca     192
Leu Arg Val Glu Pro Val Thr Thr Ser Val Ala Thr Gly Asp Tyr Ser
    35                  40                  45

att ttg atg aat gta agc tgg gta ctc cgg gca gat gcc agc atc cgc     240
Ile Leu Met Asn Val Ser Trp Val Leu Arg Ala Asp Ala Ser Ile Arg
 50                  55                  60                  65

ttg ttg aag gcc acc aag att tgt gtg acg ggc aaa agc aac ttc cag     288
Leu Leu Lys Ala Thr Lys Ile Cys Val Thr Gly Lys Ser Asn Phe Gln
                70                  75                  80

tcc tac agc tgt gtg agg tgc aat tac aca gag gcc ttc cag act cag     336
Ser Tyr Ser Cys Val Arg Cys Asn Tyr Thr Glu Ala Phe Gln Thr Gln
            85                  90                  95

acc aga ccc tct ggt ggt aaa tgg aca ttt tcc tat atc ggc ttc cct     384
Thr Arg Pro Ser Gly Gly Lys Trp Thr Phe Ser Tyr Ile Gly Phe Pro
        100                 105                 110

gta gag ctg aac aca gtc tat ttc att ggg gcc cat aat att cct aat     432
Val Glu Leu Asn Thr Val Tyr Phe Ile Gly Ala His Asn Ile Pro Asn
    115                 120                 125

gca aat atg aat gaa gat ggc cct tcc atg tct gtg aat ttc acc tca     480
Ala Asn Met Asn Glu Asp Gly Pro Ser Met Ser Val Asn Phe Thr Ser
130                 135                 140                 145

cca ggc tgc cta gac cac ata atg aaa tat aaa aaa aag tgt gtc aag     528
Pro Gly Cys Leu Asp His Ile Met Lys Tyr Lys Lys Lys Cys Val Lys
                150                 155                 160

gcc gga agc ctg tgg gat ccg aac atc act gct tgt aag aag aat gag     576
Ala Gly Ser Leu Trp Asp Pro Asn Ile Thr Ala Cys Lys Lys Asn Glu
            165                 170                 175

gag aca gta gaa gtg aac ttc aca acc act ccc ctg gga aac aga tac     624
Glu Thr Val Glu Val Asn Phe Thr Thr Thr Pro Leu Gly Asn Arg Tyr
        180                 185                 190
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atg gct ctt atc caa cac agc act atc atc ggg ttt tct cag gtg ttt    672
Met Ala Leu Ile Gln His Ser Thr Ile Ile Gly Phe Ser Gln Val Phe
    195                 200                 205

gag cca cac cag aag aaa caa acg cga gct tca gtg gtg att cca gtg    720
Glu Pro His Gln Lys Lys Gln Thr Arg Ala Ser Val Val Ile Pro Val
210                 215                 220                 225

act ggg gat agt gaa ggt gct acg gtg cag ctg act cca tat ttt cct    768
Thr Gly Asp Ser Glu Gly Ala Thr Val Gln Leu Thr Pro Tyr Phe Pro
                230                 235                 240

act tgt ggc agc gac tgc atc cga cat aaa gga aca gtt gtg ctc tgc    816
Thr Cys Gly Ser Asp Cys Ile Arg His Lys Gly Thr Val Val Leu Cys
            245                 250                 255

cca caa aca ggc gtc cct ttc cct ctg gat aac aac aaa agc aag ccg    864
Pro Gln Thr Gly Val Pro Phe Pro Leu Asp Asn Asn Lys Ser Lys Pro
        260                 265                 270

gga ggc tgg ctg cct ctc ctc ctg ctg tct ctg ctg gtg gcc aca tgg    912
Gly Gly Trp Leu Pro Leu Leu Leu Leu Ser Leu Leu Val Ala Thr Trp
    275                 280                 285

gtg ctg gtg gca ggg atc tat cta atg tgg agg cac gaa agg atc aag    960
Val Leu Val Ala Gly Ile Tyr Leu Met Trp Arg His Glu Arg Ile Lys
290                 295                 300                 305

aag act tcc ttt tct acc acc aca cta ctg ccc ccc att aag gtt ctt    1008
Lys Thr Ser Phe Ser Thr Thr Thr Leu Leu Pro Pro Ile Lys Val Leu
                310                 315                 320

gtg gtt tac cca tct gaa ata tgt ttc cat cac aca att tgt tac ttc    1056
Val Val Tyr Pro Ser Glu Ile Cys Phe His His Thr Ile Cys Tyr Phe
            325                 330                 335

act gaa ttt ctt caa aac cat tgc aga agt gag gtc atc ctt gaa aag    1104
Thr Glu Phe Leu Gln Asn His Cys Arg Ser Glu Val Ile Leu Glu Lys
        340                 345                 350

tgg cag aaa aag aaa ata gca gag atg ggt cca gtg cag tgg ctt gcc    1152
Trp Gln Lys Lys Lys Ile Ala Glu Met Gly Pro Val Gln Trp Leu Ala
    355                 360                 365

act caa aag aag gca gca gac aaa gtc gtc ttc ctt ctt tcc aat gac    1200
Thr Gln Lys Lys Ala Ala Asp Lys Val Val Phe Leu Leu Ser Asn Asp
370                 375                 380                 385

gtc aac agt gtg tgc gat ggt acc tgt ggc aag agc gag ggc agt ccc    1248
Val Asn Ser Val Cys Asp Gly Thr Cys Gly Lys Ser Glu Gly Ser Pro
                390                 395                 400

agt gag aac tct caa gac ctc ttc ccc ctt gcc ttt aac ctt ttc tgc    1296
Ser Glu Asn Ser Gln Asp Leu Phe Pro Leu Ala Phe Asn Leu Phe Cys
            405                 410                 415

agt gat cta aga agc cag att cat ctg cac aaa tac gtg gtg gtc tac    1344
Ser Asp Leu Arg Ser Gln Ile His Leu His Lys Tyr Val Val Val Tyr
        420                 425                 430
```

```
ttt aga gag att gat aca aaa gac gat tac aat gct ctc agt gtc tgc    1392
Phe Arg Glu Ile Asp Thr Lys Asp Asp Tyr Asn Ala Leu Ser Val Cys
    435                 440                 445

ccc aag tac cac ctc atg aag gat gcc act gct ttc tgt gca gaa ctt    1440
Pro Lys Tyr His Leu Met Lys Asp Ala Thr Ala Phe Cys Ala Glu Leu
450                 455                 460                 465

ctc cat gtc aag cag cag gtg tca gca gga aaa aga tca caa gcc tgc    1488
Leu His Val Lys Gln Gln Val Ser Ala Gly Lys Arg Ser Gln Ala Cys
                470                 475                 480

cac gat ggc tgc tgc tcc ttg tagcccaccc atgagaagca agagacctta       1539
His Asp Gly Cys Cys Ser Leu
            485

aaggcttcct atcccaccaa ttacagggaa aaaacgtgtg atgatcctga agcttactat 1599

gcagcctaca aacagcctta gtaattaaaa cattttatac caataaaatt ttcaaatatt 1659

gctaactaat gtagcattaa ctaacgattg gaaactacat ttacaacttc aaagctgttt 1719

tatacataga aatcaattac agctttaatt gaaaactgta accattttga taatgcaaca 1779

ataaagcatc ttcagcc                                                 1796


<210> 2
<211> 502
<212> PRT
<213> Unknown

<400> 2
Met Ser Leu Val Leu Leu Ser Leu Ala Ala Leu Cys Arg Ser Ala Val
                -10                 -5                  -1   1

Pro Arg Glu Pro Thr Val Gln Cys Gly Ser Glu Thr Gly Pro Ser Pro
            5                   10                  15

Glu Trp Met Leu Gln His Asp Leu Ile Pro Gly Asp Leu Arg Asp Leu
    20                  25                  30

Arg Val Glu Pro Val Thr Thr Ser Val Ala Thr Gly Asp Tyr Ser Ile
35                  40                  45                  50

Leu Met Asn Val Ser Trp Val Leu Arg Ala Asp Ala Ser Ile Arg Leu
                55                  60                  65

Leu Lys Ala Thr Lys Ile Cys Val Thr Gly Lys Ser Asn Phe Gln Ser
            70                  75                  80

Tyr Ser Cys Val Arg Cys Asn Tyr Thr Glu Ala Phe Gln Thr Gln Thr
        85                  90                  95

Arg Pro Ser Gly Gly Lys Trp Thr Phe Ser Tyr Ile Gly Phe Pro Val
    100                 105                 110

Glu Leu Asn Thr Val Tyr Phe Ile Gly Ala His Asn Ile Pro Asn Ala
115                 120                 125                 130
```

```
Asn Met Asn Glu Asp Gly Pro Ser Met Ser Val Asn Phe Thr Ser Pro
                135                 140                 145

Gly Cys Leu Asp His Ile Met Lys Tyr Lys Lys Lys Cys Val Lys Ala
            150                 155                 160

Gly Ser Leu Trp Asp Pro Asn Ile Thr Ala Cys Lys Lys Asn Glu Glu
        165                 170                 175

Thr Val Glu Val Asn Phe Thr Thr Thr Pro Leu Gly Asn Arg Tyr Met
    180                 185                 190

Ala Leu Ile Gln His Ser Thr Ile Ile Gly Phe Ser Gln Val Phe Glu
195                 200                 205                 210

Pro His Gln Lys Lys Gln Thr Arg Ala Ser Val Val Ile Pro Val Thr
                215                 220                 225

Gly Asp Ser Glu Gly Ala Thr Val Gln Leu Thr Pro Tyr Phe Pro Thr
            230                 235                 240

Cys Gly Ser Asp Cys Ile Arg His Lys Gly Thr Val Val Leu Cys Pro
        245                 250                 255

Gln Thr Gly Val Pro Phe Pro Leu Asp Asn Asn Lys Ser Lys Pro Gly
    260                 265                 270

Gly Trp Leu Pro Leu Leu Leu Leu Ser Leu Leu Val Ala Thr Trp Val
275                 280                 285                 290

Leu Val Ala Gly Ile Tyr Leu Met Trp Arg His Glu Arg Ile Lys Lys
                295                 300                 305

Thr Ser Phe Ser Thr Thr Thr Leu Leu Pro Pro Ile Lys Val Leu Val
            310                 315                 320

Val Tyr Pro Ser Glu Ile Cys Phe His His Thr Ile Cys Tyr Phe Thr
        325                 330                 335

Glu Phe Leu Gln Asn His Cys Arg Ser Glu Val Ile Leu Glu Lys Trp
    340                 345                 350

Gln Lys Lys Lys Ile Ala Glu Met Gly Pro Val Gln Trp Leu Ala Thr
355                 360                 365                 370

Gln Lys Lys Ala Ala Asp Lys Val Val Phe Leu Leu Ser Asn Asp Val
                375                 380                 385

Asn Ser Val Cys Asp Gly Thr Cys Gly Lys Ser Glu Gly Ser Pro Ser
            390                 395                 400

Glu Asn Ser Gln Asp Leu Phe Pro Leu Ala Phe Asn Leu Phe Cys Ser
        405                 410                 415

Asp Leu Arg Ser Gln Ile His Leu His Lys Tyr Val Val Val Tyr Phe
    420                 425                 430

Arg Glu Ile Asp Thr Lys Asp Asp Tyr Asn Ala Leu Ser Val Cys Pro
435                 440                 445                 450
```

Lys Tyr His Leu Met Lys Asp Ala Thr Ala Phe Cys Ala Glu Leu Leu
455 460 465

His Val Lys Gln Gln Val Ser Ala Gly Lys Arg Ser Gln Ala Cys His
470 475 480

Asp Gly Cys Cys Ser Leu
485

<210> 3
<211> 1506
<212> DNA
<213> reverse translation

<220>
<221> misc_feature
<222> (1)..(1506)
<223> n may be a, c, g, or t

<400> 3
atgwsnytng tnytnytnws nytngcngcn ytntgymgnw sngcngtncc nmgngarccn 60

acngtncart gyggnwsnga racnggnccn wsnccngart ggatgytnca rcaygayytn 120

athccnggng ayytnmgnga yytnmgngtn garccngtna cnacnwsngt ngcnacnggn 180

gaytaywsna thytnatgaa ygtnwsntgg gtnytnmgng cngaygcnws nathmgnytn 240

ytnaargcna cnaarathtg ygtnacnggn aarwsnaayt tycarwsnta ywsntgygtn 300

mgntgyaayt ayacngargc nttycaracn caracnmgnc cnwsnggngg naartggacn 360

ttywsntaya thggnttycc ngtngarytn aayacngtnt ayttyathgg ngcncayaay 420

athccnaayg cnaayatgaa ygargayggn ccnwsnatgw sngtnaaytt yacnwsnccn 480

ggntgyytng aycayathat gaartayaar aaraartgyg tnaargcngg nwsnytntgg 540

gayccnaaya thacngcntg yaaraaraay gargaracng tngargtnaa yttyacnacn 600

acnccnytng gnaaymgnta yatggcnytn athcarcayw snacnathat hggnttywsn 660

cargtnttyg arccncayca raaraarcar acnmgngcnw sngtngtnat hccngtnacn 720

ggngaywsng arggngcnac ngtncarytn acnccntayt tyccnacntg yggnwsngay 780

tgyathmgnc ayaarggnac ngtngtnytn tgyccncara cnggngtncc nttyccnytn 840

gayaayaaya arwsnaarcc nggnggntgg ytnccnytny tnytnytnws nytnytngtn 900

gcnacntggg tnytngtngc nggnathtay ytnatgtggm gncaygarmg nathaaraar 960

acnwsnttyw snacnacnac nytnytnccn ccnathaarg tnytngtngt ntayccnwsn 1020

garathtgyt tycaycayac nathtgytay ttyacngart tyytncaraa ycaytgymgn 1080

wsngargtna thytngaraa rtggcaraar aaraarathg cngaratggg nccngtncar 1140

tggytngcna cncaraaraa rgcngcngay aargtngtnt tyytnytnws naaygaygtn 1200

aaywsngtnt gygayggnac ntgyggnaar wsngarggnw snccnwsnga raaywsncar 1260

gayytnttyc cnytngcntt yaayytntty tgywsngayy tnmgnwsnca rathcayytn 1320

cayaartayg tngtngtnta yttymgngar athgayacna argaygayta yaaygcnytn 1380

wsngtntgyc cnaartayca yytnatgaar gaygcnacng cnttytgygc ngarytnytn 1440

caygtnaarc arcargtnws ngcnggnaar mgnwsncarg cntgycayga yggntgytgy 1500

wsnytn 1506

<210> 4
<211> 637
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:rodent; surmised
Mus musculus .

<220>
<221> CDS
<222> (1)..(210)

<400> 4
gat ttc agc agc cag acg cat ctg cac aaa tac ctg gag gtc tat ctt 48
Asp Phe Ser Ser Gln Thr His Leu His Lys Tyr Leu Glu Val Tyr Leu
1 5 10 15

ggg gga gca gac ctc aaa ggc gac tat aat gcc ctg agt gtc tgc ccc 96
Gly Gly Ala Asp Leu Lys Gly Asp Tyr Asn Ala Leu Ser Val Cys Pro
20 25 30

caa tat cat ctc atg aag gac gcc aca gct ttc cac aca gaa ctt ctc 144
Gln Tyr His Leu Met Lys Asp Ala Thr Ala Phe His Thr Glu Leu Leu
35 40 45

aag gct acg cag agc atg tca gtg aag aaa cgc tca caa gcc tgc cat 192
Lys Ala Thr Gln Ser Met Ser Val Lys Lys Arg Ser Gln Ala Cys His
50 55 60

gat agc tgt tca ccc ttg tagtccaccc gggggaatag agactctgaa 240
Asp Ser Cys Ser Pro Leu
65 70

gccttcctac tctcccttcc agtgacaaat gctgtgtgac gactctgaaa tgtgtgggag 300

aggctgtgtg gaggtagtgc tatgtacaaa cttgctttaa aactggagtt tgcaaagtca 360

acctgagcat acacgcctga ggctagtcat tggctggatt tatgaagaca acacagttac 420

agacaataat gagtgggacc tacatttggg atatacccaa agctgggtaa tgattatcac 480

tgagaaccac gcactctggc catgaggtaa tacggcactt ccctgtcagg ctgtctgtca 540

ggttgggtct gtcttgcact gcccatgctc tatgctgcac gtagaccgtt ttgtaacatt 600

ttaatctgtt aatgaataat ccgtttggga ggctctc 637

<210> 5
<211> 70
<212> PRT
<213> Unknown

<400> 5
Asp Phe Ser Ser Gln Thr His Leu His Lys Tyr Leu Glu Val Tyr Leu
1 5 10 15

Gly Gly Ala Asp Leu Lys Gly Asp Tyr Asn Ala Leu Ser Val Cys Pro
20 25 30

Gln Tyr His Leu Met Lys Asp Ala Thr Ala Phe His Thr Glu Leu Leu
35 40 45

Lys Ala Thr Gln Ser Met Ser Val Lys Lys Arg Ser Gln Ala Cys His
50 55 60

Asp Ser Cys Ser Pro Leu
65 70

<210> 6
<211> 210
<212> DNA
<213> reverse translation

<220>
<221> misc_feature
<222> (1)..(210)
<223> n may be a, c, g, or t

<400> 6
gayttywsnw sncaracnca yytncayaar tayytngarg tntayytngg nggngcngay 60

ytnaarggng aytayaaygc nytnwsngtn tgyccncart aycayytnat gaargaygcn 120

acngcnttyc ayacngaryt nytnaargcn acncarwsna tgwsngtnaa raarmgnwsn 180

cargcntgyc aygaywsntg ywsnccnytn 210

<210> 7
<211> 2308
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:primate; surmised
Homo sapiens

<220>
<221> CDS
<222> (181)..(2289)

<220>

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<221> mat_peptide
<222> (241)..(2289)

<220>
<221> misc_feature
<222> (664)
<223> Xaa translation depends on genetic code

<400> 7
gagtcaggac tcccaggaca gagagtgcac aaactaccca gcacagcccc ctccgccccc 60

tctggaggct gaagagggat tccagcccct gccacccaca gacacgggct gactggggtg 120

tctgcccccc ttgggggcan ccacagggcc tcaggcctgg gtgccacctg gcactagaag 180

atg cct gtg ccc tgg ttc ttg ctg tcc ttg gca ctg ggc cga agc cag    228
Met Pro Val Pro Trp Phe Leu Leu Ser Leu Ala Leu Gly Arg Ser Gln
-20                 -15                 -10                 -5

tgg atc ctt tct ctg gag agg ctt gtg ggg cct cag gac gct acc cac    276
Trp Ile Leu Ser Leu Glu Arg Leu Val Gly Pro Gln Asp Ala Thr His
            -1   1               5                  10

tgc tct ccg ggc ctc tcc tgc cgc ctc tgg gac agt gac ata ctc tgc    324
Cys Ser Pro Gly Leu Ser Cys Arg Leu Trp Asp Ser Asp Ile Leu Cys
        15                  20                  25

ctg cct ggg gac atc gtg cct gct ccg ggc ccc gtg ctg gcg cct acg    372
Leu Pro Gly Asp Ile Val Pro Ala Pro Gly Pro Val Leu Ala Pro Thr
    30                  35                  40

cac ctg cag aca gag ctg gtg ctg agg tgc cag aag gag acc gac tgt    420
His Leu Gln Thr Glu Leu Val Leu Arg Cys Gln Lys Glu Thr Asp Cys
45                  50                  55                  60

gac ctc tgt ctg cgt gtg gct gtc cac ttg gcc gtg cat ggg cac tgg    468
Asp Leu Cys Leu Arg Val Ala Val His Leu Ala Val His Gly His Trp
                65                  70                  75

gaa gag cct gaa gat gag gaa aag ttt gga gga gca gct gac tta ggg    516
Glu Glu Pro Glu Asp Glu Glu Lys Phe Gly Gly Ala Ala Asp Leu Gly
            80                  85                  90

gtg gag gag cct agg aat gcc tct ctc cag gcc caa gtc gtg ctc tcc    564
Val Glu Glu Pro Arg Asn Ala Ser Leu Gln Ala Gln Val Val Leu Ser
        95                  100                 105

ttc cag gcc tac cct act gcc cgc tgc gtc ctg ctg gag gtg caa gtg    612
Phe Gln Ala Tyr Pro Thr Ala Arg Cys Val Leu Leu Glu Val Gln Val
    110                 115                 120

cct gct gcc ctt gtg cag ttt ggt cag tct gtg ggc tct gtg gta tat    660
Pro Ala Ala Leu Val Gln Phe Gly Gln Ser Val Gly Ser Val Val Tyr
125                 130                 135                 140

gac tgc ttc gag gct gcc cta ggg agt gag gta cga atc tgg tcc tat    708
Asp Cys Phe Glu Ala Ala Leu Gly Ser Glu Val Arg Ile Trp Ser Tyr
                145                 150                 155

act cag ccc agg tac gag aag gaa ctc aac cac aca cag cag ctg cct    756
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Thr Gln Pro Arg Tyr Glu Lys Glu Leu Asn His Thr Gln Gln Leu Pro
            160                 165                 170

gac tgc agg ggg ctc gaa gtc tgg aac agc atc ccg agc tgc tgg gcc      804
Asp Cys Arg Gly Leu Glu Val Trp Asn Ser Ile Pro Ser Cys Trp Ala
        175                 180                 185

ctg ccc tgg ctc aac gtg tca gca gat ggt gac aac gtg cat ctg gtt      852
Leu Pro Trp Leu Asn Val Ser Ala Asp Gly Asp Asn Val His Leu Val
    190                 195                 200

ctg aat gtc tct gag gag cag cac ttc ggc ctc tcc ctg tac tgg aat      900
Leu Asn Val Ser Glu Glu Gln His Phe Gly Leu Ser Leu Tyr Trp Asn
205                 210                 215                 220

cag gtc cag ggc ccc cca aaa ccc cgg tgg cac aaa aac ctg act gga      948
Gln Val Gln Gly Pro Pro Lys Pro Arg Trp His Lys Asn Leu Thr Gly
                225                 230                 235

ccg cag atc att acc ttg aac cac aca gac ctg gtt ccc tgc ctc tgt      996
Pro Gln Ile Ile Thr Leu Asn His Thr Asp Leu Val Pro Cys Leu Cys
            240                 245                 250

att cag gtg tgg cct ctg gaa cct gac tcc gtt agg acg aac atc tgc     1044
Ile Gln Val Trp Pro Leu Glu Pro Asp Ser Val Arg Thr Asn Ile Cys
        255                 260                 265

ccc ttc agg gag gac ccc cgc gca cac cag aac ctc tgg caa gcc gcc     1092
Pro Phe Arg Glu Asp Pro Arg Ala His Gln Asn Leu Trp Gln Ala Ala
    270                 275                 280

cga ctg cga ctg ctg acc ctg cag agc tgg ctg ctg gac gca ccg tgc     1140
Arg Leu Arg Leu Leu Thr Leu Gln Ser Trp Leu Leu Asp Ala Pro Cys
285                 290                 295                 300

tcg ctg ccc gca gaa gcg gca ctg tgc tgg cgg gct ccg ggt ggg gac     1188
Ser Leu Pro Ala Glu Ala Ala Leu Cys Trp Arg Ala Pro Gly Gly Asp
                305                 310                 315

ccc tgc cag cca ctg gtc cca ccg ctt tcc tgg gag aat gtc act gtg     1236
Pro Cys Gln Pro Leu Val Pro Pro Leu Ser Trp Glu Asn Val Thr Val
            320                 325                 330

gac gtg aac agc tcg gag aag ctg cag ctg cag gag tgc ttg tgg gct     1284
Asp Val Asn Ser Ser Glu Lys Leu Gln Leu Gln Glu Cys Leu Trp Ala
        335                 340                 345

gac tcc ctg ggg cct ctc aaa gac gat gtg cta ctg ttg gag aca cga     1332
Asp Ser Leu Gly Pro Leu Lys Asp Asp Val Leu Leu Leu Glu Thr Arg
    350                 355                 360

ggc ccc cag gac aac aga tcc ctc tgt gcc ttg gaa ccc agt ggc tgt     1380
Gly Pro Gln Asp Asn Arg Ser Leu Cys Ala Leu Glu Pro Ser Gly Cys
365                 370                 375                 380

act tca cta ccc agc aaa gcc tcc acg agg gca gct cgc ctt gga gag     1428
Thr Ser Leu Pro Ser Lys Ala Ser Thr Arg Ala Ala Arg Leu Gly Glu
                385                 390                 395

tac tta cta caa gac ctg cag tca ggc cag tgt ctg cag cta tgg gac     1476
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```
Tyr Leu Leu Gln Asp Leu Gln Ser Gly Gln Cys Leu Gln Leu Trp Asp
            400                 405                 410

gat gac ttg gga gcg cta tgg gcc tgc ccc atg gac aaa tac atc cac      1524
Asp Asp Leu Gly Ala Leu Trp Ala Cys Pro Met Asp Lys Tyr Ile His
        415                 420                 425

aag cgc tgg gcc ctc gtg tgg ctg gcc tgc cta ctc ttt gcc gct gcg      1572
Lys Arg Trp Ala Leu Val Trp Leu Ala Cys Leu Leu Phe Ala Ala Ala
    430                 435                 440

ctt tcc ctc atc ctc ctt ctc aaa aag gat cac gcg aaa ggg tgg ctg      1620
Leu Ser Leu Ile Leu Leu Leu Lys Lys Asp His Ala Lys Gly Trp Leu
445                 450                 455                 460

agg ctc ttg aaa cag gac gtc cgc tcg ggg gcg gcc gcc agg ggc cgc      1668
Arg Leu Leu Lys Gln Asp Val Arg Ser Gly Ala Ala Ala Arg Gly Arg
                465                 470                 475

gcg gct ctg ctc ctc tac tca gcc gat gac tcg ggt ttc gag cgc ctg      1716
Ala Ala Leu Leu Leu Tyr Ser Ala Asp Asp Ser Gly Phe Glu Arg Leu
            480                 485                 490

gtg ggc gcc ctg gcg tcg gcc ctg tgc cag ctg ccg ctg cgc gtg gcc      1764
Val Gly Ala Leu Ala Ser Ala Leu Cys Gln Leu Pro Leu Arg Val Ala
        495                 500                 505

gta gac ctg tgg agc cgt cgt gaa ctg agc gcg cag ggg ccc gtg gct      1812
Val Asp Leu Trp Ser Arg Arg Glu Leu Ser Ala Gln Gly Pro Val Ala
    510                 515                 520

tgg ttt cac gcg cag cgg cgc cag acc ctg cag gag ggc ggc gtg gtg      1860
Trp Phe His Ala Gln Arg Arg Gln Thr Leu Gln Glu Gly Gly Val Val
525                 530                 535                 540

gtc ttg ctc ttc tct ccc ggt gcg gtg gcg ctg tgc agc gag tgg cta      1908
Val Leu Leu Phe Ser Pro Gly Ala Val Ala Leu Cys Ser Glu Trp Leu
                545                 550                 555

cag gat ggg gtg tcc ggg ccc ggg gcg cac ggc ccg cac gac gcc ttc      1956
Gln Asp Gly Val Ser Gly Pro Gly Ala His Gly Pro His Asp Ala Phe
            560                 565                 570

cgc gcc tcg ctc agc tgc gtg ctg ccc gac ttc ttg cag ggc cgg gcg      2004
Arg Ala Ser Leu Ser Cys Val Leu Pro Asp Phe Leu Gln Gly Arg Ala
        575                 580                 585

ccc ggc agc tac gtg ggg gcc tgc ttc gac agg ctg ctc cac ccg gac      2052
Pro Gly Ser Tyr Val Gly Ala Cys Phe Asp Arg Leu Leu His Pro Asp
    590                 595                 600

gcc gta ccc gcc ctt ttc cgc acc gtg ccc gtc ttc aca ctg ccc tcc      2100
Ala Val Pro Ala Leu Phe Arg Thr Val Pro Val Phe Thr Leu Pro Ser
605                 610                 615                 620

caa ctg cca gac ttc ctg ggg gcc ctg cag cag cct cgc gcc ccg cgt      2148
Gln Leu Pro Asp Phe Leu Gly Ala Leu Gln Gln Pro Arg Ala Pro Arg
                625                 630                 635

tcc ggg cgg ctc caa gag aga gcg gag caa gtg tcc cgg gcc ctt cag      2196
```

```
Ser Gly Arg Leu Gln Glu Arg Ala Glu Gln Val Ser Arg Ala Leu Gln
            640                 645                 650

cca gcc ctg gat agc tac ttc cat ccc ccg ggg acn tcc gcg ccg gga    2244
Pro Ala Leu Asp Ser Tyr Phe His Pro Pro Gly Xaa Ser Ala Pro Gly
        655                 660                 665

cgc ggg gtg gga cca ggg gcg gga cct ggg gcg ggg gac ggg act        2289
Arg Gly Val Gly Pro Gly Ala Gly Pro Gly Ala Gly Asp Gly Thr
    670                 675                 680

taaataaagg cagacgctg                                               2308


<210> 8
<211> 703
<212> PRT
<213> Unknown

<400> 8
Met Pro Val Pro Trp Phe Leu Leu Ser Leu Ala Leu Gly Arg Ser Gln
-20                 -15                 -10                  -5

Trp Ile Leu Ser Leu Glu Arg Leu Val Gly Pro Gln Asp Ala Thr His
            -1   1                   5                  10

Cys Ser Pro Gly Leu Ser Cys Arg Leu Trp Asp Ser Asp Ile Leu Cys
        15                  20                  25

Leu Pro Gly Asp Ile Val Pro Ala Pro Gly Pro Val Leu Ala Pro Thr
    30                  35                  40

His Leu Gln Thr Glu Leu Val Leu Arg Cys Gln Lys Glu Thr Asp Cys
 45                  50                  55                  60

Asp Leu Cys Leu Arg Val Ala Val His Leu Ala Val His Gly His Trp
                65                  70                  75

Glu Glu Pro Glu Asp Glu Glu Lys Phe Gly Gly Ala Ala Asp Leu Gly
            80                  85                  90

Val Glu Glu Pro Arg Asn Ala Ser Leu Gln Ala Gln Val Val Leu Ser
        95                 100                 105

Phe Gln Ala Tyr Pro Thr Ala Arg Cys Val Leu Leu Glu Val Gln Val
    110                 115                 120

Pro Ala Ala Leu Val Gln Phe Gly Gln Ser Val Gly Ser Val Val Tyr
125                 130                 135                 140

Asp Cys Phe Glu Ala Ala Leu Gly Ser Glu Val Arg Ile Trp Ser Tyr
                145                 150                 155

Thr Gln Pro Arg Tyr Glu Lys Glu Leu Asn His Thr Gln Gln Leu Pro
            160                 165                 170

Asp Cys Arg Gly Leu Glu Val Trp Asn Ser Ile Pro Ser Cys Trp Ala
        175                 180                 185

Leu Pro Trp Leu Asn Val Ser Ala Asp Gly Asp Asn Val His Leu Val
```

190 195 200

Leu Asn Val Ser Glu Glu Gln His Phe Gly Leu Ser Leu Tyr Trp Asn
205 210 215 220

Gln Val Gln Gly Pro Pro Lys Pro Arg Trp His Lys Asn Leu Thr Gly
225 230 235

Pro Gln Ile Ile Thr Leu Asn His Thr Asp Leu Val Pro Cys Leu Cys
240 245 250

Ile Gln Val Trp Pro Leu Glu Pro Asp Ser Val Arg Thr Asn Ile Cys
255 260 265

Pro Phe Arg Glu Asp Pro Arg Ala His Gln Asn Leu Trp Gln Ala Ala
270 275 280

Arg Leu Arg Leu Leu Thr Leu Gln Ser Trp Leu Leu Asp Ala Pro Cys
285 290 295 300

Ser Leu Pro Ala Glu Ala Ala Leu Cys Trp Arg Ala Pro Gly Gly Asp
305 310 315

Pro Cys Gln Pro Leu Val Pro Pro Leu Ser Trp Glu Asn Val Thr Val
320 325 330

Asp Val Asn Ser Ser Glu Lys Leu Gln Leu Gln Glu Cys Leu Trp Ala
335 340 345

Asp Ser Leu Gly Pro Leu Lys Asp Asp Val Leu Leu Leu Glu Thr Arg
350 355 360

Gly Pro Gln Asp Asn Arg Ser Leu Cys Ala Leu Glu Pro Ser Gly Cys
365 370 375 380

Thr Ser Leu Pro Ser Lys Ala Ser Thr Arg Ala Ala Arg Leu Gly Glu
385 390 395

Tyr Leu Leu Gln Asp Leu Gln Ser Gly Gln Cys Leu Gln Leu Trp Asp
400 405 410

Asp Asp Leu Gly Ala Leu Trp Ala Cys Pro Met Asp Lys Tyr Ile His
415 420 425

Lys Arg Trp Ala Leu Val Trp Leu Ala Cys Leu Leu Phe Ala Ala Ala
430 435 440

Leu Ser Leu Ile Leu Leu Leu Lys Lys Asp His Ala Lys Gly Trp Leu
445 450 455 460

Arg Leu Leu Lys Gln Asp Val Arg Ser Gly Ala Ala Ala Arg Gly Arg
465 470 475

Ala Ala Leu Leu Leu Tyr Ser Ala Asp Asp Ser Gly Phe Glu Arg Leu
480 485 490

Val Gly Ala Leu Ala Ser Ala Leu Cys Gln Leu Pro Leu Arg Val Ala
495 500 505

Val Asp Leu Trp Ser Arg Arg Glu Leu Ser Ala Gln Gly Pro Val Ala

510 515 520

Trp Phe His Ala Gln Arg Arg Gln Thr Leu Gln Glu Gly Gly Val Val
525 530 535 540

Val Leu Leu Phe Ser Pro Gly Ala Val Ala Leu Cys Ser Glu Trp Leu
545 550 555

Gln Asp Gly Val Ser Gly Pro Gly Ala His Gly Pro His Asp Ala Phe
560 565 570

Arg Ala Ser Leu Ser Cys Val Leu Pro Asp Phe Leu Gln Gly Arg Ala
575 580 585

Pro Gly Ser Tyr Val Gly Ala Cys Phe Asp Arg Leu Leu His Pro Asp
590 595 600

Ala Val Pro Ala Leu Phe Arg Thr Val Pro Val Phe Thr Leu Pro Ser
605 610 615 620

Gln Leu Pro Asp Phe Leu Gly Ala Leu Gln Gln Pro Arg Ala Pro Arg
625 630 635

Ser Gly Arg Leu Gln Glu Arg Ala Glu Gln Val Ser Arg Ala Leu Gln
640 645 650

Pro Ala Leu Asp Ser Tyr Phe His Pro Pro Gly Xaa Ser Ala Pro Gly
655 660 665

Arg Gly Val Gly Pro Gly Ala Gly Pro Gly Ala Gly Asp Gly Thr
670 675 680

<210> 9
<211> 2109
<212> DNA
<213> reverse translation

<220>
<221> misc_feature
<222> (1)..(2109)
<223> n may be a, c, g, or t

<400> 9
atgccngtnc cntggttyyt nytnwsnytn gcnytnggnm gnwsncartg gathytnwsn 60

ytngarmgny tngtnggncc ncargaygcn acncaytgyw snccnggnyt nwsntgymgn 120

ytntgggayw sngayathyt ntgyytnccn ggngayathg tnccngcncc nggnccngtn 180

ytngcnccna cncayytnca racngarytn gtnytnmgnt gycaraarga racngaytgy 240

gayytntgyy tnmgngtngc ngtncayytn gcngtncayg gncaytggga rgarccngar 300

gaygargara arttyggngg ngcngcngay ytnggngtng argarccnmg naaygcnwsn 360

ytncargcnc argtngtnyt nwsnttycar gcntayccna cngcnmgntg ygtnytnytn 420

gargtncarg tnccngcngc nytngtncar ttyggncarw sngtnggnws ngtngtntay 480

gaytgyttyg argcngcnyt nggnwsngar gtnmgnatht ggwsntayac ncarccnmgn 540
taygaraarg arytnaayca yacncarcar ytnccngayt gymgnggnyt ngargtntgg 600
aaywsnathc cnwsntgytg ggcnytnccn tggytnaayg tnwsngcnga yggngayaay 660
gtncayytng tnytnaaygt nwsngargar carcayttyg gnytnwsnyt ntaytggaay 720
cargtncarg gnccnccnaa rccnmgntgg cayaaraayy tnacnggncc ncarathath 780
acnytnaayc ayacngayyt ngtnccntgy ytntgyathc argtntggcc nytngarccn 840
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tggcargcng cnmgnytnmg nytnytnacn ytncarwsnt ggytnytnga ygcnccntgy 960
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carytncarg artgyytntg ggcngaywsn ytnggnccny tnaargayga ygtnytnytn 1140
ytngaracnm gnggnccnca rgayaaymgn wsnytntgyg cnytngarcc nwsnggntgy 1200
acnwsnytnc cnwsnaargc nwsnacnmgn gcngcnmgny tnggngarta yytnytncar 1260
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ttygcngcng cnytnwsnyt nathytnytn ytnaaraarg aycaygcnaa rggntggytn 1440
mgnytnytna arcargaygt nmgnwsnggn gcngcngcnm gnggnmgngc ngcnytnytn 1500
ytntaywsng cngaygayws nggnttygar mgnytngtng gngcnytngc nwsngcnytn 1560
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ggnccngtng cntggttyca ygcncarmgn mgncaracny tncargargg nggngtngtn 1680
gtnytnytnt tywsnccngg ngcngtngcn ytntgywsng artggytnca rgayggngtn 1740
wsnggnccng gngcncaygg nccncaygay gcnttymgng cnwsnytnws ntgygtnytn 1800
ccngayttyy tncarggnmg ngcnccnggn wsntaygtng gngcntgytt ygaymgnytn 1860
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carytnccng ayttyytngg ngcnytncar carccnmgng cnccnmgnws nggnmgnytn 1980
cargarmgng cngarcargt nwsnmgngcn ytncarccng cnytngayws ntayttycay 2040
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gayggnacn 2109

<210> 10
<211> 2314
<212> DNA

<213> Unknown

<220>
<223> Description of Unknown Organism:rodent; surmised
Mus musculus

<220>
<221> CDS
<222> (199)..(2292)

<220>
<221> mat_peptide
<222> (259)..(2292)

<400> 10

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agcaggggcg aggggtctgc ccccccttgg gggggcagga cggggcctca ggcctgggtg 180

ctgtccggca cctggaag atg cct gtg tcc tgg ttc ctg ctg tcc ttg gca   231
                    Met Pro Val Ser Trp Phe Leu Leu Ser Leu Ala
                    -20                 -15                 -10

ctg ggc cga aac cct gtg gtc gtc tct ctg gag aga ctg atg gag cct   279
Leu Gly Arg Asn Pro Val Val Val Ser Leu Glu Arg Leu Met Glu Pro
                -5                  -1   1               5

cag gac act gca cgc tgc tct cta ggc ctc tcc tgc cac ctc tgg gat   327
Gln Asp Thr Ala Arg Cys Ser Leu Gly Leu Ser Cys His Leu Trp Asp
        10                  15                  20

ggt gac gtg ctc tgc ctg cct gga agc ctc cag tct gcc cca ggc cct   375
Gly Asp Val Leu Cys Leu Pro Gly Ser Leu Gln Ser Ala Pro Gly Pro
    25                  30                  35

gtg cta gtg cct acc cgc ctg cag acg gag ctg gtg ctg agg tgt cca   423
Val Leu Val Pro Thr Arg Leu Gln Thr Glu Leu Val Leu Arg Cys Pro
40                  45                  50                  55

cag aag aca gat tgc gcc ctc tgt gtc cgt gtg gtg gtc cac ttg gcc   471
Gln Lys Thr Asp Cys Ala Leu Cys Val Arg Val Val Val His Leu Ala
                60                  65                  70

gtg cat ggg cac tgg gca gag cct gaa gaa gct gga aag tct gat tca   519
Val His Gly His Trp Ala Glu Pro Glu Glu Ala Gly Lys Ser Asp Ser
            75                  80                  85

gaa ctc cag gag tct agg aac gcc tct ctc cag gcc cag gtg gtg ctc   567
Glu Leu Gln Glu Ser Arg Asn Ala Ser Leu Gln Ala Gln Val Val Leu
        90                  95                  100

tcc ttc cag gcc tac ccc atc gcc cgc tgt gcc ctg ctg gag gtc cag   615
Ser Phe Gln Ala Tyr Pro Ile Ala Arg Cys Ala Leu Leu Glu Val Gln
    105                 110                 115

gtg ccc gct gac ctg gtg cag cct ggt cag tcc gtg ggt tct gcg gta   663
Val Pro Ala Asp Leu Val Gln Pro Gly Gln Ser Val Gly Ser Ala Val
120                 125                 130                 135
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ttt gac tgt ttc gag gct agt ctt ggg gct gag gta cag atc tgg tcc    711
Phe Asp Cys Phe Glu Ala Ser Leu Gly Ala Glu Val Gln Ile Trp Ser
            140                 145                 150

tac acg aag ccc agg tac cag aaa gag ctc aac ctc aca cag cag ctg    759
Tyr Thr Lys Pro Arg Tyr Gln Lys Glu Leu Asn Leu Thr Gln Gln Leu
        155                 160                 165

cct gac tgc agg ggt ctt gaa gtc cgg gac agc atc cag agc tgc tgg    807
Pro Asp Cys Arg Gly Leu Glu Val Arg Asp Ser Ile Gln Ser Cys Trp
    170                 175                 180

gtc ctg ccc tgg ctc aat gtg tct aca gat ggt gac aat gtc ctt ctg    855
Val Leu Pro Trp Leu Asn Val Ser Thr Asp Gly Asp Asn Val Leu Leu
185                 190                 195

aca ctg gat gtc tct gag gag cag gac ttt agc ttc tta ctg tac ctg    903
Thr Leu Asp Val Ser Glu Glu Gln Asp Phe Ser Phe Leu Leu Tyr Leu
200                 205                 210                 215

cgt cca gtc ccg gat gct ctc aaa tcc ttg tgg tac aaa aac ctg act    951
Arg Pro Val Pro Asp Ala Leu Lys Ser Leu Trp Tyr Lys Asn Leu Thr
                220                 225                 230

gga cct cag aac att act tta aac cac aca gac ctg gtt ccc tgc ctc    999
Gly Pro Gln Asn Ile Thr Leu Asn His Thr Asp Leu Val Pro Cys Leu
            235                 240                 245

tgc att cag gtg tgg tcg cta gag cca gac tct gag agg gtc gaa ttc    1047
Cys Ile Gln Val Trp Ser Leu Glu Pro Asp Ser Glu Arg Val Glu Phe
        250                 255                 260

tgc ccc ttc cgg gaa gat ccc ggt gca cac agg aac ctc tgg cac ata    1095
Cys Pro Phe Arg Glu Asp Pro Gly Ala His Arg Asn Leu Trp His Ile
    265                 270                 275

gcc agg ctg cgg gta ctg tcc cca ggg gta tgg cag cta gat gcg cct    1143
Ala Arg Leu Arg Val Leu Ser Pro Gly Val Trp Gln Leu Asp Ala Pro
280                 285                 290                 295

tgc tgt ctg ccg ggc aag gta aca ctg tgc tgg cag gca cca gac cag    1191
Cys Cys Leu Pro Gly Lys Val Thr Leu Cys Trp Gln Ala Pro Asp Gln
                300                 305                 310

agt ccc tgc cag cca ctt gtg cca cca gtg ccc cag aag aac gcc act    1239
Ser Pro Cys Gln Pro Leu Val Pro Pro Val Pro Gln Lys Asn Ala Thr
            315                 320                 325

gtg aat gag cca caa gat ttc cag ttg gtg gca ggc cac ccc aac ctc    1287
Val Asn Glu Pro Gln Asp Phe Gln Leu Val Ala Gly His Pro Asn Leu
        330                 335                 340

tgt gtc cag gtg agc acc tgg gag aag gtt cag ctg caa gcg tgc ttg    1335
Cys Val Gln Val Ser Thr Trp Glu Lys Val Gln Leu Gln Ala Cys Leu
    345                 350                 355

tgg gct gac tcc ttg ggg ccc ttc aag gat gat atg ctg tta gtg gag    1383
Trp Ala Asp Ser Leu Gly Pro Phe Lys Asp Asp Met Leu Leu Val Glu
360                 365                 370                 375
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atg aaa acc ggc ctc aac aac aca tca gtc tgt gcc ttg gaa ccc agt    1431
Met Lys Thr Gly Leu Asn Asn Thr Ser Val Cys Ala Leu Glu Pro Ser
                380                 385                 390

ggc tgt aca cca ctg ccc agc atg gcc tcc acg aga gct gct cgc ctg    1479
Gly Cys Thr Pro Leu Pro Ser Met Ala Ser Thr Arg Ala Ala Arg Leu
            395                 400                 405

gga gag gag ttg ctg caa gac ttc cga tca cac cag tgt atg cag ctg    1527
Gly Glu Glu Leu Leu Gln Asp Phe Arg Ser His Gln Cys Met Gln Leu
        410                 415                 420

tgg aac gat gac aac atg gga tcg cta tgg gcc tgc ccc atg gac aag    1575
Trp Asn Asp Asp Asn Met Gly Ser Leu Trp Ala Cys Pro Met Asp Lys
    425                 430                 435

tac atc cac agg cgc tgg gtc cta gta tgg ctg gcc tgc cta ctc ttg    1623
Tyr Ile His Arg Arg Trp Val Leu Val Trp Leu Ala Cys Leu Leu Leu
440                 445                 450                 455

gct gcg gcg ctt ttc ttc ttc ctc ctt cta aaa aag gac cgc agg aaa    1671
Ala Ala Ala Leu Phe Phe Phe Leu Leu Leu Lys Lys Asp Arg Arg Lys
                460                 465                 470

gcg gcc cgt ggc tcc cgc acg gcc ttg ctc ctc cac tcc gcc gac gga    1719
Ala Ala Arg Gly Ser Arg Thr Ala Leu Leu Leu His Ser Ala Asp Gly
            475                 480                 485

gcg ggc tac gag cgc ctg gtg gga gca ctg gcg tcc gcg ttg agc cag    1767
Ala Gly Tyr Glu Arg Leu Val Gly Ala Leu Ala Ser Ala Leu Ser Gln
        490                 495                 500

atg cca ctg cgc gtg gcc gtg gac ctg tgg agc cgc cgc gag ctg agc    1815
Met Pro Leu Arg Val Ala Val Asp Leu Trp Ser Arg Arg Glu Leu Ser
    505                 510                 515

gcg cac gga gcc cta gcc tgg ttc cac cac cag cga cgc cgt atc ctg    1863
Ala His Gly Ala Leu Ala Trp Phe His His Gln Arg Arg Arg Ile Leu
520                 525                 530                 535

cag gag ggt ggc gtg gta atc ctt ctc ttc tcg ccc gcg gcc gtg gcg    1911
Gln Glu Gly Gly Val Val Ile Leu Leu Phe Ser Pro Ala Ala Val Ala
                540                 545                 550

cag tgt cag cag tgg ctg cag ctc cag aca gtg gag ccc ggg ccg cat    1959
Gln Cys Gln Gln Trp Leu Gln Leu Gln Thr Val Glu Pro Gly Pro His
            555                 560                 565

gac gcc ctc gcc gcc tgg ctc agc tgc gtg cta ccc gat ttc ctg caa    2007
Asp Ala Leu Ala Ala Trp Leu Ser Cys Val Leu Pro Asp Phe Leu Gln
        570                 575                 580

ggc cgg gcg acc ggc cgc tac gtc ggg gtc tac ttc gac ggg ctg ctg    2055
Gly Arg Ala Thr Gly Arg Tyr Val Gly Val Tyr Phe Asp Gly Leu Leu
    585                 590                 595

cac cca gac tct gtg ccc tcc ccg ttc cgc gtc gcc ccg ctc ttc tcc    2103
His Pro Asp Ser Val Pro Ser Pro Phe Arg Val Ala Pro Leu Phe Ser
600                 605                 610                 615
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ctg ccc tcg cag ctg ccg gct ttc ctg gat gca ctg cag gga ggc tgc     2151
Leu Pro Ser Gln Leu Pro Ala Phe Leu Asp Ala Leu Gln Gly Gly Cys
                620                     625                 630

tcc act tcc gcg ggg cga ccc gcg gac cgg gtg gaa cga gtg acc cag     2199
Ser Thr Ser Ala Gly Arg Pro Ala Asp Arg Val Glu Arg Val Thr Gln
            635                 640                     645

gcg ctg cgg tcc gcc ctg gac agc tgt act tct agc tcg gaa gcc cca     2247
Ala Leu Arg Ser Ala Leu Asp Ser Cys Thr Ser Ser Ser Glu Ala Pro
        650                 655                 660

ggc tgc tgc gag gaa tgg gac ctg gga ccc tgc act aca cta gaa         2292
Gly Cys Cys Glu Glu Trp Asp Leu Gly Pro Cys Thr Thr Leu Glu
    665                 670                 675

taaaagccga tacagtattc ct                                            2314


<210> 11
<211> 698
<212> PRT
<213> Unknown

<400> 11
Met Pro Val Ser Trp Phe Leu Leu Ser Leu Ala Leu Gly Arg Asn Pro
-20                 -15                 -10                  -5

Val Val Val Ser Leu Glu Arg Leu Met Glu Pro Gln Asp Thr Ala Arg
             -1   1               5                  10

Cys Ser Leu Gly Leu Ser Cys His Leu Trp Asp Gly Asp Val Leu Cys
        15                  20                  25

Leu Pro Gly Ser Leu Gln Ser Ala Pro Gly Pro Val Leu Val Pro Thr
    30                  35                  40

Arg Leu Gln Thr Glu Leu Val Leu Arg Cys Pro Gln Lys Thr Asp Cys
45                  50                  55                  60

Ala Leu Cys Val Arg Val Val Val His Leu Ala Val His Gly His Trp
                65                  70                  75

Ala Glu Pro Glu Glu Ala Gly Lys Ser Asp Ser Glu Leu Gln Glu Ser
            80                  85                  90

Arg Asn Ala Ser Leu Gln Ala Gln Val Val Leu Ser Phe Gln Ala Tyr
        95                  100                 105

Pro Ile Ala Arg Cys Ala Leu Leu Glu Val Gln Val Pro Ala Asp Leu
    110                 115                 120

Val Gln Pro Gly Gln Ser Val Gly Ser Ala Val Phe Asp Cys Phe Glu
125                 130                 135                 140

Ala Ser Leu Gly Ala Glu Val Gln Ile Trp Ser Tyr Thr Lys Pro Arg
                145                 150                 155

Tyr Gln Lys Glu Leu Asn Leu Thr Gln Gln Leu Pro Asp Cys Arg Gly
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            160                 165                 170

Leu Glu Val Arg Asp Ser Ile Gln Ser Cys Trp Val Leu Pro Trp Leu
        175                 180                 185

Asn Val Ser Thr Asp Gly Asp Asn Val Leu Leu Thr Leu Asp Val Ser
    190                 195                 200

Glu Glu Gln Asp Phe Ser Phe Leu Leu Tyr Leu Arg Pro Val Pro Asp
205                 210                 215                 220

Ala Leu Lys Ser Leu Trp Tyr Lys Asn Leu Thr Gly Pro Gln Asn Ile
                225                 230                 235

Thr Leu Asn His Thr Asp Leu Val Pro Cys Leu Cys Ile Gln Val Trp
            240                 245                 250

Ser Leu Glu Pro Asp Ser Glu Arg Val Glu Phe Cys Pro Phe Arg Glu
        255                 260                 265

Asp Pro Gly Ala His Arg Asn Leu Trp His Ile Ala Arg Leu Arg Val
    270                 275                 280

Leu Ser Pro Gly Val Trp Gln Leu Asp Ala Pro Cys Cys Leu Pro Gly
285                 290                 295                 300

Lys Val Thr Leu Cys Trp Gln Ala Pro Asp Gln Ser Pro Cys Gln Pro
                305                 310                 315

Leu Val Pro Pro Val Pro Gln Lys Asn Ala Thr Val Asn Glu Pro Gln
            320                 325                 330

Asp Phe Gln Leu Val Ala Gly His Pro Asn Leu Cys Val Gln Val Ser
        335                 340                 345

Thr Trp Glu Lys Val Gln Leu Gln Ala Cys Leu Trp Ala Asp Ser Leu
    350                 355                 360

Gly Pro Phe Lys Asp Asp Met Leu Leu Val Glu Met Lys Thr Gly Leu
365                 370                 375                 380

Asn Asn Thr Ser Val Cys Ala Leu Glu Pro Ser Gly Cys Thr Pro Leu
                385                 390                 395

Pro Ser Met Ala Ser Thr Arg Ala Ala Arg Leu Gly Glu Glu Leu Leu
            400                 405                 410

Gln Asp Phe Arg Ser His Gln Cys Met Gln Leu Trp Asn Asp Asp Asn
        415                 420                 425

Met Gly Ser Leu Trp Ala Cys Pro Met Asp Lys Tyr Ile His Arg Arg
    430                 435                 440

Trp Val Leu Val Trp Leu Ala Cys Leu Leu Leu Ala Ala Ala Leu Phe
445                 450                 455                 460

Phe Phe Leu Leu Leu Lys Lys Asp Arg Arg Lys Ala Ala Arg Gly Ser
                465                 470                 475

Arg Thr Ala Leu Leu Leu His Ser Ala Asp Gly Ala Gly Tyr Glu Arg
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480 485 490

Leu Val Gly Ala Leu Ala Ser Ala Leu Ser Gln Met Pro Leu Arg Val
495 500 505

Ala Val Asp Leu Trp Ser Arg Arg Glu Leu Ser Ala His Gly Ala Leu
510 515 520

Ala Trp Phe His His Gln Arg Arg Arg Ile Leu Gln Glu Gly Gly Val
525 530 535 540

Val Ile Leu Leu Phe Ser Pro Ala Ala Val Ala Gln Cys Gln Gln Trp
545 550 555

Leu Gln Leu Gln Thr Val Glu Pro Gly Pro His Asp Ala Leu Ala Ala
560 565 570

Trp Leu Ser Cys Val Leu Pro Asp Phe Leu Gln Gly Arg Ala Thr Gly
575 580 585

Arg Tyr Val Gly Val Tyr Phe Asp Gly Leu Leu His Pro Asp Ser Val
590 595 600

Pro Ser Pro Phe Arg Val Ala Pro Leu Phe Ser Leu Pro Ser Gln Leu
605 610 615 620

Pro Ala Phe Leu Asp Ala Leu Gln Gly Gly Cys Ser Thr Ser Ala Gly
625 630 635

Arg Pro Ala Asp Arg Val Glu Arg Val Thr Gln Ala Leu Arg Ser Ala
640 645 650

Leu Asp Ser Cys Thr Ser Ser Ser Glu Ala Pro Gly Cys Cys Glu Glu
655 660 665

Trp Asp Leu Gly Pro Cys Thr Thr Leu Glu
670 675

<210> 12
<211> 2094
<212> DNA
<213> reverse translation

<220>
<221> misc_feature
<222> (1)..(2094)
<223> n may be a, c, g, or t

<400> 12
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ytngarmgny tnatggarcc ncargayacn gcnmgntgyw snytnggnyt nwsntgycay 120

ytntgggayg gngaygtnyt ntgyytnccn ggnwsnytnc arwsngcncc nggnccngtn 180

ytngtnccna cnmgnytnca racngarytn gtnytnmgnt gyccncaraa racngaytgy 240

gcnytntgyg tnmgngtngt ngtncayytn gcngtncayg gncaytgggc ngarccngar 300

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gargcnggna arwsngayws ngarytncar garwsnmgna aygcnwsnyt ncargcncar 360
gtngtnytnw snttycargc ntayccnath gcnmgntgyg cnytnytnga rgtncargtn 420
ccngcngayy tngtncarcc nggncarwsn gtnggnwsng cngtnttyga ytgyttygar 480
gcnwsnytng gngcngargt ncarathtgg wsntayacna arccnmgnta ycaraargar 540
ytnaayytna cncarcaryt nccngaytgy mgnggnytng argtnmgnga ywsnathcar 600
wsntgytggg tnytnccntg gytnaaygtn wsnacngayg gngayaaygt nytnytnacn 660
ytngaygtnw sngargarca rgayttywsn ttyytnytnt ayytnmgncc ngtnccngay 720
gcnytnaarw snytntggta yaaraayytn acnggnccnc araayathac nytnaaycay 780
acngayytng tnccntgyyt ntgyathcar gtntggwsny tngarccnga ywsngarmgn 840
gtngarttyt gyccnttymg ngargayccn ggngcncaym gnaayytntg gcayathgcn 900
mgnytnmgng tnytnwsncc nggngtntgg carytngayg cnccntgytg yytnccnggn 960
aargtnacny tntgytggca rgcnccngay carwsnccnt gycarccnyt ngtnccnccn 1020
gtnccncara araaygcnac ngtnaaygar ccncargayt tycarytngt ngcnggncay 1080
ccnaayytnt gygtncargt nwsnacntgg garaargtnc arytncargc ntgyytntgg 1140
gcngaywsny tnggnccntt yaargaygay atgytnytng tngaratgaa racnggnytn 1200
aayaayacnw sngtntgygc nytngarccn wsnggntgya cnccnytncc nwsnatggcn 1260
wsnacnmgng cngcnmgnyt nggngargar ytnytncarg ayttymgnws ncaycartgy 1320
atgcarytnt ggaaygayga yaayatgggn wsnytntggg cntgyccnat ggayaartay 1380
athcaymgnm gntgggtnyt ngtntggytn gcntgyytny tnytngcngc ngcnytntty 1440
ttyttyytny tnytnaaraa rgaymgnmgn aargcngcnm gnggnwsnmg nacngcnytn 1500
ytnytncayw sngcngaygg ngcnggntay garmgnytng tnggngcnyt ngcnwsngcn 1560
ytnwsncara tgccnytnmg ngtngcngtn gayytntggw snmgnmgnga rytnwsngcn 1620
cayggngcny tngcntggtt ycaycaycar mgnmgnmgna thytncarga rggnggngtn 1680
gtnathytny tnttywsncc ngcngcngtn gcncartgyc arcartggyt ncarytncar 1740
acngtngarc cnggnccnca ygaygcnytn gcngcntggy tnwsntgygt nytnccngay 1800
ttyytncarg gnmgngcnac nggnmgntay gtnggngtnt ayttygaygg nytnytncay 1860
ccngaywsng tnccnwsncc nttymgngtn gcnccnytnt tywsnytncc nwsncarytn 1920
ccngcnttyy tngaygcnyt ncarggnggn tgywsnacnw sngcnggnmg nccngcngay 1980
mgngtngarm gngtnacnca rgcnytnmgn wsngcnytng aywsntgyac nwsnwsnwsn 2040
gargcnccng gntgytgyga rgartgggay ytnggnccnt gyacnacnyt ngar       2094
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<210> 13
<211> 2786
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:primate; surmised
      Homo sapiens

<220>
<221> CDS
<222> (70)..(2283)

<220>
<221> mat_peptide
<222> (118)..(2283)

<220>
<221> misc_feature
<222> (9)..(134)
<223> Xaa translation (9, 18,26, 109,120, 134) depends
      on genetic code

<400> 13
cccacgcntc cgggccagca gcgggcggcc ggggcgcaga gaacggcctg gctgggcgag 60

cgcacggcc atg gcc ccg tgg ctg cag ctc tgc tcc gtc ttc ttt acg gtc 111
          Met Ala Pro Trp Leu Gln Leu Cys Ser Val Phe Phe Thr Val
              -15                 -10                     -5

aac gcc tgc ctc aac ggc tcg cag ctg gct gtn gcc gct ggc ggg tcc   159
Asn Ala Cys Leu Asn Gly Ser Gln Leu Ala Xaa Ala Ala Gly Gly Ser
     -1   1               5                  10

ggc cgc gcg cng ggc gcc gac acc tgt agc tgg ang gga gtg ggg cca   207
Gly Arg Ala Xaa Gly Ala Asp Thr Cys Ser Trp Xaa Gly Val Gly Pro
 15                  20                  25                  30

gcc agc aga aac agt ggg ctg tac aac atc acc ttc aaa tat gac aat   255
Ala Ser Arg Asn Ser Gly Leu Tyr Asn Ile Thr Phe Lys Tyr Asp Asn
                 35                  40                  45

tgt acc acc tac ttg aat cca gtg ggg aag cat gtg att gct gac gcc   303
Cys Thr Thr Tyr Leu Asn Pro Val Gly Lys His Val Ile Ala Asp Ala
             50                  55                  60

cag aat atc acc atc agc cag tat gct tgc cat gac caa gtg gca gtc   351
Gln Asn Ile Thr Ile Ser Gln Tyr Ala Cys His Asp Gln Val Ala Val
         65                  70                  75

acc att ctt tgg tcc cca ggg gcc ctc ggc atc gaa ttc ctg aaa gga   399
Thr Ile Leu Trp Ser Pro Gly Ala Leu Gly Ile Glu Phe Leu Lys Gly
     80                  85                  90

ttt cgg gta ata ctg gag gag ctg aag tcg gag gga aga cag ngc caa   447
Phe Arg Val Ile Leu Glu Glu Leu Lys Ser Glu Gly Arg Gln Xaa Gln
 95                 100                 105                 110

caa ctg att cta aag gat ccg aag cag ntc aac agt agc ttc aaa aga   495
```

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Gln Leu Ile Leu Lys Asp Pro Lys Gln Xaa Asn Ser Ser Phe Lys Arg
                115                 120                 125

act gga atg gaa tct caa cct ttn ctg aat atg aaa ttt gaa acg gat     543
Thr Gly Met Glu Ser Gln Pro Xaa Leu Asn Met Lys Phe Glu Thr Asp
            130                 135                 140

tat ttc gta agg ttg tcc ttt tcc ttc att aaa aac gaa agc aat tac     591
Tyr Phe Val Arg Leu Ser Phe Ser Phe Ile Lys Asn Glu Ser Asn Tyr
        145                 150                 155

cac cct ttc ttc ttt aga acc cga gcc tgt gac ctg ttg tta cag ccg     639
His Pro Phe Phe Phe Arg Thr Arg Ala Cys Asp Leu Leu Leu Gln Pro
    160                 165                 170

gac aat cta gct tgt aaa ccc ttc tgg aag cct cgg aac ctg aac atc     687
Asp Asn Leu Ala Cys Lys Pro Phe Trp Lys Pro Arg Asn Leu Asn Ile
175                 180                 185                 190

agc cag cat ggc tcg gac atg cag gtg tcc ttc gac cac gca ccg cac     735
Ser Gln His Gly Ser Asp Met Gln Val Ser Phe Asp His Ala Pro His
                195                 200                 205

aac ttc ggc ttc cgt ttc ttc tat ctt cac tac aag ctc aag cac gaa     783
Asn Phe Gly Phe Arg Phe Phe Tyr Leu His Tyr Lys Leu Lys His Glu
            210                 215                 220

gga cct ttc aag cga aag acc tgt aag cag gag caa act aca gag atg     831
Gly Pro Phe Lys Arg Lys Thr Cys Lys Gln Glu Gln Thr Thr Glu Met
        225                 230                 235

acc agc tgc ctc ctt caa aat gtt tct cca ggg gat tat ata att gag     879
Thr Ser Cys Leu Leu Gln Asn Val Ser Pro Gly Asp Tyr Ile Ile Glu
    240                 245                 250

ctg gtg gat gac act aac aca aca aga aaa gtg atg cat tat gcc tta     927
Leu Val Asp Asp Thr Asn Thr Thr Arg Lys Val Met His Tyr Ala Leu
255                 260                 265                 270

aag cca gtg cac tcc ccg tgg gcc ggg ccc atc aga gcc gtg gcc atc     975
Lys Pro Val His Ser Pro Trp Ala Gly Pro Ile Arg Ala Val Ala Ile
                275                 280                 285

aca gtg cca ctg gta gtc ata tcg gca ttc gcg acg ctc ttc act gtg     1023
Thr Val Pro Leu Val Val Ile Ser Ala Phe Ala Thr Leu Phe Thr Val
            290                 295                 300

atg tgc cgc aag aag caa caa gaa aat ata tat tca cat tta gat gaa     1071
Met Cys Arg Lys Lys Gln Gln Glu Asn Ile Tyr Ser His Leu Asp Glu
        305                 310                 315

gag agc tct gag tct tcc aca tac act gca gca ctc cca aga gag agg     1119
Glu Ser Ser Glu Ser Ser Thr Tyr Thr Ala Ala Leu Pro Arg Glu Arg
    320                 325                 330

ctc cgg ccg cgg ccg aag gtc ttt ctc tgc tat tcc agt aaa gat ggc     1167
Leu Arg Pro Arg Pro Lys Val Phe Leu Cys Tyr Ser Ser Lys Asp Gly
335                 340                 345                 350

cag aat cac atg aat gtc gtc cag tgt ttc gcc tac ttc ctc cag gac     1215
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```
Gln Asn His Met Asn Val Val Gln Cys Phe Ala Tyr Phe Leu Gln Asp
                355                 360                 365

ttc tgt ggc tgt gag gtg gct ctg gac ctg tgg gaa gac ttc agc ctc      1263
Phe Cys Gly Cys Glu Val Ala Leu Asp Leu Trp Glu Asp Phe Ser Leu
            370                 375                 380

tgt aga gaa ggg cag aga gaa tgg gtc atc cag aag atc cac gag tcc      1311
Cys Arg Glu Gly Gln Arg Glu Trp Val Ile Gln Lys Ile His Glu Ser
        385                 390                 395

cag ttc atc att gtg gtt tgt tcc aaa ggt atg aag tac ttt gtg gac      1359
Gln Phe Ile Ile Val Val Cys Ser Lys Gly Met Lys Tyr Phe Val Asp
    400                 405                 410

aag aag aac tac aaa cac aaa gga ggt ggc cga ggc tcg ggg aaa gga      1407
Lys Lys Asn Tyr Lys His Lys Gly Gly Gly Arg Gly Ser Gly Lys Gly
415                 420                 425                 430

gag ctc ttc ctg gtg gcg gtg tca gcc att gcc gaa aag ctc cgc cag      1455
Glu Leu Phe Leu Val Ala Val Ser Ala Ile Ala Glu Lys Leu Arg Gln
                435                 440                 445

gcc aag cag agt tcg tcc gcg gcg ctc agc aag ttt atc gcc gtc tac      1503
Ala Lys Gln Ser Ser Ser Ala Ala Leu Ser Lys Phe Ile Ala Val Tyr
            450                 455                 460

ttt gat tat tcc tgc gag gga gac gtc ccc ggt atc cta gac ctg agt      1551
Phe Asp Tyr Ser Cys Glu Gly Asp Val Pro Gly Ile Leu Asp Leu Ser
        465                 470                 475

acc aag tac aga ctc atg gac aat ctt cct cag ctc tgt tcc cac ctg      1599
Thr Lys Tyr Arg Leu Met Asp Asn Leu Pro Gln Leu Cys Ser His Leu
    480                 485                 490

cac tcc cga gac cac ggc ctc cag gag ccg ggg cag cac acg cga cag      1647
His Ser Arg Asp His Gly Leu Gln Glu Pro Gly Gln His Thr Arg Gln
495                 500                 505                 510

ggc agc aga agg aac tac ttc cgg agc aag tca ggc cgg tcc cta tac      1695
Gly Ser Arg Arg Asn Tyr Phe Arg Ser Lys Ser Gly Arg Ser Leu Tyr
                515                 520                 525

gtc gcc att tgc aac atg cac cag ttt att gac gag gag ccc gac tgg      1743
Val Ala Ile Cys Asn Met His Gln Phe Ile Asp Glu Glu Pro Asp Trp
            530                 535                 540

ttc gaa aag cag ttc gtt ccc ttc cat cct cct cca ctg cgc tac cgg      1791
Phe Glu Lys Gln Phe Val Pro Phe His Pro Pro Pro Leu Arg Tyr Arg
        545                 550                 555

gag cca gtc ttg gag aaa ttt gat tcg ggc ttg gtt tta aat gat gtc      1839
Glu Pro Val Leu Glu Lys Phe Asp Ser Gly Leu Val Leu Asn Asp Val
    560                 565                 570

atg tgc aaa cca ggg cct gag agt gac ttc tgc cta aag gta gag gcg      1887
Met Cys Lys Pro Gly Pro Glu Ser Asp Phe Cys Leu Lys Val Glu Ala
575                 580                 585                 590

gct gtt ctt ggg gca acc gga cca gcc gac tcc cag cac gag agt cag      1935
```

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Ala Val Leu Gly Ala Thr Gly Pro Ala Asp Ser Gln His Glu Ser Gln
                595                 600                 605

cat ggg ggc ctg gac caa gac ggg gag gcc cgg cct gcc ctt gac ggt    1983
His Gly Gly Leu Asp Gln Asp Gly Glu Ala Arg Pro Ala Leu Asp Gly
            610                 615                 620

agc gcc gcc ctg caa ccc ctg ctg cac acg gtg aaa gcc ggc agc ccc    2031
Ser Ala Ala Leu Gln Pro Leu Leu His Thr Val Lys Ala Gly Ser Pro
        625                 630                 635

tcg gac atg ccg cgg gac tca ggc atc tat gac tcg tct gtg ccc tca    2079
Ser Asp Met Pro Arg Asp Ser Gly Ile Tyr Asp Ser Ser Val Pro Ser
    640                 645                 650

tcc gag ctg tct ctg cca ctg atg gaa gga ctc tcg acg gac cag aca    2127
Ser Glu Leu Ser Leu Pro Leu Met Glu Gly Leu Ser Thr Asp Gln Thr
655                 660                 665                 670

gaa acg tct tcc ctg acg gag agc gtg tcc tcc tct tca ggc ctg ggt    2175
Glu Thr Ser Ser Leu Thr Glu Ser Val Ser Ser Ser Ser Gly Leu Gly
                675                 680                 685

gag gag gaa cct cct gcc ctt cct tcc aag ctc ctc tct tct ggg tca    2223
Glu Glu Glu Pro Pro Ala Leu Pro Ser Lys Leu Leu Ser Ser Gly Ser
            690                 695                 700

tgc aaa gca gat ctt ggt tgc cgc agc tac act gat gaa ctc cac gcg    2271
Cys Lys Ala Asp Leu Gly Cys Arg Ser Tyr Thr Asp Glu Leu His Ala
        705                 710                 715

gtc gcc cct ttg taacaaaacg aaagagtcta agcattgcca ctttagctgc        2323
Val Ala Pro Leu
    720

tgcctccctc tgattcccca gctcatctcc ctggttgcat ggcccacttg gagctgaggt 2383

ctcatacaag gatatttgga gtgaaatgct ggccagtact tgttctccct tgccccaacc 2443

ctttaccgga tatcttgaca aactctccaa ttttctaaaa tgatatggag ctctgaaagg 2503

catgtccata aggtctgaca acagcttgcc aaatttggtt agtccttgga tcagagcctg 2563

ttgtgggagg tagggaggaa atatgtaaag aaaaacagga agatacctgc actaatcatt 2623

cagacttcat tgagctctgc aaactttgcc tgtttgctat tggctacctt gatttgaaat 2683

gctttgtgaa aaaaggcact tttaacatca tagccacaga aatcaagtgc cagtctatct 2743

ggaatccatg ttgtattgca gataatgttc tcatttattt ttg                   2786
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<210> 14
<211> 738
<212> PRT
<213> Unknown

<400> 14

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Met Ala Pro Trp Leu Gln Leu Cys Ser Val Phe Phe Thr Val Asn Ala
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Cys Leu Asn Gly Ser Gln Leu Ala Xaa Ala Ala Gly Gly Ser Gly Arg
 1               5                  10                  15

Ala Xaa Gly Ala Asp Thr Cys Ser Trp Xaa Gly Val Gly Pro Ala Ser
            20                  25                  30

Arg Asn Ser Gly Leu Tyr Asn Ile Thr Phe Lys Tyr Asp Asn Cys Thr
        35                  40                  45

Thr Tyr Leu Asn Pro Val Gly Lys His Val Ile Ala Asp Ala Gln Asn
    50                  55                  60

Ile Thr Ile Ser Gln Tyr Ala Cys His Asp Gln Val Ala Val Thr Ile
65                  70                  75                  80

Leu Trp Ser Pro Gly Ala Leu Gly Ile Glu Phe Leu Lys Gly Phe Arg
                85                  90                  95

Val Ile Leu Glu Glu Leu Lys Ser Glu Gly Arg Gln Xaa Gln Gln Leu
            100                 105                 110

Ile Leu Lys Asp Pro Lys Gln Xaa Asn Ser Ser Phe Lys Arg Thr Gly
        115                 120                 125

Met Glu Ser Gln Pro Xaa Leu Asn Met Lys Phe Glu Thr Asp Tyr Phe
    130                 135                 140

Val Arg Leu Ser Phe Ser Phe Ile Lys Asn Glu Ser Asn Tyr His Pro
145                 150                 155                 160

Phe Phe Phe Arg Thr Arg Ala Cys Asp Leu Leu Leu Gln Pro Asp Asn
                165                 170                 175

Leu Ala Cys Lys Pro Phe Trp Lys Pro Arg Asn Leu Asn Ile Ser Gln
            180                 185                 190

His Gly Ser Asp Met Gln Val Ser Phe Asp His Ala Pro His Asn Phe
        195                 200                 205

Gly Phe Arg Phe Phe Tyr Leu His Tyr Lys Leu Lys His Glu Gly Pro
    210                 215                 220

Phe Lys Arg Lys Thr Cys Lys Gln Glu Gln Thr Thr Glu Met Thr Ser
225                 230                 235                 240

Cys Leu Leu Gln Asn Val Ser Pro Gly Asp Tyr Ile Ile Glu Leu Val
                245                 250                 255

Asp Asp Thr Asn Thr Thr Arg Lys Val Met His Tyr Ala Leu Lys Pro
            260                 265                 270

Val His Ser Pro Trp Ala Gly Pro Ile Arg Ala Val Ala Ile Thr Val
        275                 280                 285

Pro Leu Val Val Ile Ser Ala Phe Ala Thr Leu Phe Thr Val Met Cys
    290                 295                 300

Arg Lys Lys Gln Gln Glu Asn Ile Tyr Ser His Leu Asp Glu Glu Ser
305                 310                 315                 320
```

Ser Glu Ser Ser Thr Tyr Thr Ala Ala Leu Pro Arg Glu Arg Leu Arg
325 330 335

Pro Arg Pro Lys Val Phe Leu Cys Tyr Ser Ser Lys Asp Gly Gln Asn
340 345 350

His Met Asn Val Val Gln Cys Phe Ala Tyr Phe Leu Gln Asp Phe Cys
355 360 365

Gly Cys Glu Val Ala Leu Asp Leu Trp Glu Asp Phe Ser Leu Cys Arg
370 375 380

Glu Gly Gln Arg Glu Trp Val Ile Gln Lys Ile His Glu Ser Gln Phe
385 390 395 400

Ile Ile Val Val Cys Ser Lys Gly Met Lys Tyr Phe Val Asp Lys Lys
405 410 415

Asn Tyr Lys His Lys Gly Gly Gly Arg Gly Ser Gly Lys Gly Glu Leu
420 425 430

Phe Leu Val Ala Val Ser Ala Ile Ala Glu Lys Leu Arg Gln Ala Lys
435 440 445

Gln Ser Ser Ser Ala Ala Leu Ser Lys Phe Ile Ala Val Tyr Phe Asp
450 455 460

Tyr Ser Cys Glu Gly Asp Val Pro Gly Ile Leu Asp Leu Ser Thr Lys
465 470 475 480

Tyr Arg Leu Met Asp Asn Leu Pro Gln Leu Cys Ser His Leu His Ser
485 490 495

Arg Asp His Gly Leu Gln Glu Pro Gly Gln His Thr Arg Gln Gly Ser
500 505 510

Arg Arg Asn Tyr Phe Arg Ser Lys Ser Gly Arg Ser Leu Tyr Val Ala
515 520 525

Ile Cys Asn Met His Gln Phe Ile Asp Glu Glu Pro Asp Trp Phe Glu
530 535 540

Lys Gln Phe Val Pro Phe His Pro Pro Pro Leu Arg Tyr Arg Glu Pro
545 550 555 560

Val Leu Glu Lys Phe Asp Ser Gly Leu Val Leu Asn Asp Val Met Cys
565 570 575

Lys Pro Gly Pro Glu Ser Asp Phe Cys Leu Lys Val Glu Ala Ala Val
580 585 590

Leu Gly Ala Thr Gly Pro Ala Asp Ser Gln His Glu Ser Gln His Gly
595 600 605

Gly Leu Asp Gln Asp Gly Glu Ala Arg Pro Ala Leu Asp Gly Ser Ala
610 615 620

Ala Leu Gln Pro Leu Leu His Thr Val Lys Ala Gly Ser Pro Ser Asp
625 630 635 640

```
Met Pro Arg Asp Ser Gly Ile Tyr Asp Ser Ser Val Pro Ser Ser Glu
                645                 650                 655

Leu Ser Leu Pro Leu Met Glu Gly Leu Ser Thr Asp Gln Thr Glu Thr
            660                 665                 670

Ser Ser Leu Thr Glu Ser Val Ser Ser Ser Ser Gly Leu Gly Glu Glu
        675                 680                 685

Glu Pro Pro Ala Leu Pro Ser Lys Leu Leu Ser Ser Gly Ser Cys Lys
    690                 695                 700

Ala Asp Leu Gly Cys Arg Ser Tyr Thr Asp Glu Leu His Ala Val Ala
705                 710                 715                 720

Pro Leu
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<210> 15
<211> 2214
<212> DNA
<213> reverse translation

<220>
<221> misc_feature
<222> (1)..(2214)
<223> n may be a, c, g, or t

<400> 15

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atggcnccnt ggytncaryt ntgywsngtn ttyttyacng tnaaygcntg yytnaayggn 60

wsncarytng cngtngcngc nggnggnwsn ggnmgngcnn nnggngcnga yacntgywsn 120

tggnnnggng tnggnccngc nwsnmgnaay wsnggnytnt ayaayathac nttyaartay 180

gayaaytgya cnacntayyt naayccngtn ggnaarcayg tnathgcnga ygcncaraay 240

athacnathw sncartaygc ntgycaygay cargtngcng tnacnathyt ntggwsnccn 300

ggngcnytng gnathgartt yytnaarggn ttymgngtna thytngarga rytnaarwsn 360

garggnmgnc arnnncarca rytnathytn aargayccna arcarnnnaa ywsnwsntty 420

aarmgnacng gnatggarws ncarccnnnn ytnaayatga arttygarac ngaytaytty 480

gtnmgnytnw snttywsntt yathaaraay garwsnaayt aycayccntt yttyttymgn 540

acnmgngcnt gygayytnyt nytncarccn gayaayytng cntgyaarcc nttytggaar 600

ccnmgnaayy tnaayathws ncarcayggn wsngayatgc argtnwsntt ygaycaygcn 660

ccncayaayt tyggnttymg nttyttytay ytncaytaya arytnaarca ygarggnccn 720

ttyaarmgna aracntgyaa rcargarcar acnacngara tgacnwsntg yytnytncar 780

aaygtnwsnc cnggngayta yathathgar ytngtngayg ayacnaayac nacnmgnaar 840

gtnatgcayt aygcnytnaa rccngtncay wsnccntggg cnggnccnat hmgngcngtn 900
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gcnathacng tnccnytngt ngtnathwsn gcnttygcna cnytnttyac ngtnatgtgy 960

mgnaararaarc arcargaraa yathtaywsn cayytngayg argarwsnws ngarwsnwsn 1020

acntayacng cngcnytncc nmgngarmgn ytnmgnccnm gnccnaargt nttyytntgy 1080

taywsnwsna argayggnca raaycayatg aaygtngtnc artgyttygc ntayttyytn 1140

cargayttyt gyggntgyga rgtngcnytn gayytntggg argayttyws nytntgymgn 1200

garggncarm gngartgggt nathcaraar athcaygarw sncarttyat hathgtngtn 1260

tgywsnaarg gnatgaarta yttygtngay aaraaraayt ayaarcayaa rggnggnggn 1320

mgnggnwsng gnaarggnga rytnttyytn gtngcngtnw sngcnathgc ngaraarytn 1380

mgncargcna arcarwsnws nwsngcngcn ytnwsnaart tyathgcngt ntayttygay 1440

taywsntgyg arggngaygt nccnggnath ytngayytnw snacnaarta ymgnytnatg 1500

gayaayytnc cncarytntg ywsncayytn caywsnmgng aycayggnyt ncargarccn 1560

ggncarcaya cnmgncargg nwsnmgnmgn aaytayttym gnwsnaarws nggnmgnwsn 1620

ytntaygtng cnathtgyaa yatgcaycar ttyathgayg argarccnga ytggttygar 1680

aarcarttyg tnccnttyca yccnccnccn ytnmgntaym gngarccngt nytngaraar 1740

ttygaywsng gnytngtnyt naaygaygtn atgtgyaarc cnggnccnga rwsngaytty 1800

tgyytnaarg tngargcngc ngtnytnggn gcnacnggnc cngcngayws ncarcaygar 1860

wsncarcayg gnggnytnga ycargayggn gargcnmgnc cngcnytnga yggnwsngcn 1920

gcnytncarc cnytnytnca yacngtnaar gcnggnwsnc cnwsngayat gccnmgngay 1980

wsnggnatht aygaywsnws ngtnccnwsn wsngarytnw snytnccnyt natggarggn 2040

ytnwsnacng aycaracnga racnwsnwsn ytnacngarw sngtnwsnws nwsnwsnggn 2100

ytnggngarg argarccncc ngcnytnccn wsnaarytny tnwsnwsngg nwsntgyaar 2160

gcngayytng gntgymgnws ntayacngay garytncayg cngtngcncc nytn 2214

<210> 16
<211> 2012
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:primate; surmised
Homo sapiens

<220>
<221> CDS
<222> (1)..(1971)

<220>

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<221> mat_peptide
<222> (70)..(1971)

<400> 16
atg ggg agc tcc aga ctg gca gcc ctg ctc ctg cct ctc ctc ctc ata      48
Met Gly Ser Ser Arg Leu Ala Ala Leu Leu Leu Pro Leu Leu Leu Ile
            -20                 -15                 -10

gtc atc gac ctc tct gac tct gct ggg att ggc ttt cgc cac ctg ccc      96
Val Ile Asp Leu Ser Asp Ser Ala Gly Ile Gly Phe Arg His Leu Pro
         -5              -1   1               5

cac tgg aac acc cgc tgt cct ctg gcc tcc cac acg gaa gtt ctg cct      144
His Trp Asn Thr Arg Cys Pro Leu Ala Ser His Thr Glu Val Leu Pro
 10                  15                  20                  25

ata tcc ctt gcc gca cct ggt ggg ccc tct tct cca caa agc ctt ggt      192
Ile Ser Leu Ala Ala Pro Gly Gly Pro Ser Ser Pro Gln Ser Leu Gly
                 30                  35                  40

gtg tgc gag tct ggc act gtt ccc gct gtt tgt gcc agc atc tgc tgt      240
Val Cys Glu Ser Gly Thr Val Pro Ala Val Cys Ala Ser Ile Cys Cys
             45                  50                  55

cag gtg gct cag gtc ttc aac ggg gcc tct tcc acc tcc tgg tgc aga      288
Gln Val Ala Gln Val Phe Asn Gly Ala Ser Ser Thr Ser Trp Cys Arg
         60                  65                  70

aat cca aaa agt ctt cca cat tca agt tct ata gga gac aca aga tgc      336
Asn Pro Lys Ser Leu Pro His Ser Ser Ser Ile Gly Asp Thr Arg Cys
     75                  80                  85

cag cac ctg ctc aga gga agc tgc tgc ctc gtc gtc acc tgt ctg aga      384
Gln His Leu Leu Arg Gly Ser Cys Cys Leu Val Val Thr Cys Leu Arg
 90                  95                 100                 105

aga gcc atc aca ttt cca tcc cct ccc cag aca tct ccc aca agg gac      432
Arg Ala Ile Thr Phe Pro Ser Pro Pro Gln Thr Ser Pro Thr Arg Asp
                110                 115                 120

ttc gct cta aaa gga ccc aac ctt cgg atc cag aga cat ggg aaa gtc      480
Phe Ala Leu Lys Gly Pro Asn Leu Arg Ile Gln Arg His Gly Lys Val
            125                 130                 135

ttc cca gat tgg act cac aaa ggc atg gag gtg ggc act ggg tac aac      528
Phe Pro Asp Trp Thr His Lys Gly Met Glu Val Gly Thr Gly Tyr Asn
        140                 145                 150

agg aga tgg gtt cag ctg agt ggt gga ccc gag ttc tcc ttt gat ttg      576
Arg Arg Trp Val Gln Leu Ser Gly Gly Pro Glu Phe Ser Phe Asp Leu
    155                 160                 165

ctg cct gag gcc cgg gct att cgg gtg acc ata tct tca ggc cct gag      624
Leu Pro Glu Ala Arg Ala Ile Arg Val Thr Ile Ser Ser Gly Pro Glu
170                 175                 180                 185

gtc agc gtg cgt ctt tgt cac cag tgg gca ctg gag tgt gaa gag ctg      672
Val Ser Val Arg Leu Cys His Gln Trp Ala Leu Glu Cys Glu Glu Leu
                190                 195                 200
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agc agt ccc tat gat gtc cag aaa att gtg tct ggg ggc cac act gta     720
Ser Ser Pro Tyr Asp Val Gln Lys Ile Val Ser Gly Gly His Thr Val
            205                 210                 215

gag ctg cct tat gaa ttc ctt ctg ccc tgt ctg tgc ata gag gca tcc     768
Glu Leu Pro Tyr Glu Phe Leu Leu Pro Cys Leu Cys Ile Glu Ala Ser
        220                 225                 230

tac ctg caa gag gac act gtg agg cgc aaa aaa tgt ccc ttc cag agc     816
Tyr Leu Gln Glu Asp Thr Val Arg Arg Lys Lys Cys Pro Phe Gln Ser
    235                 240                 245

tgg cca gaa gcc tat ggc tcg gac ttc tgg aag tca gtg cac ttc act     864
Trp Pro Glu Ala Tyr Gly Ser Asp Phe Trp Lys Ser Val His Phe Thr
250                 255                 260                 265

gac tac agc cag cac act cag atg gtc atg gcc ctg aca ctc cgc tgc     912
Asp Tyr Ser Gln His Thr Gln Met Val Met Ala Leu Thr Leu Arg Cys
                270                 275                 280

cca ctg aag ctg gaa gct gcc ctc tgc cag agg cac gac tgg cat acc     960
Pro Leu Lys Leu Glu Ala Ala Leu Cys Gln Arg His Asp Trp His Thr
            285                 290                 295

ctt tgc aaa gac ctc ccg aat gcc acg gct cga gag tca gat ggg tgg     1008
Leu Cys Lys Asp Leu Pro Asn Ala Thr Ala Arg Glu Ser Asp Gly Trp
        300                 305                 310

tat gtt ttg gag aag gtg gac ctg cac ccc cag ctc tgc ttc aag gta     1056
Tyr Val Leu Glu Lys Val Asp Leu His Pro Gln Leu Cys Phe Lys Val
    315                 320                 325

caa cca tgg ttc tct ttt gga aac agc agc cat gtt gaa tgc ccc cac     1104
Gln Pro Trp Phe Ser Phe Gly Asn Ser Ser His Val Glu Cys Pro His
330                 335                 340                 345

cag act ggg tct ctc aca tcc tgg aat gta agc atg gat acc caa gcc     1152
Gln Thr Gly Ser Leu Thr Ser Trp Asn Val Ser Met Asp Thr Gln Ala
                350                 355                 360

cag cag ctg att ctt cac ttc tcc tca aga atg cat gcc acc ttc agt     1200
Gln Gln Leu Ile Leu His Phe Ser Ser Arg Met His Ala Thr Phe Ser
            365                 370                 375

gct gcc tgg agc ctc cca ggc ttg ggg cag gac act ttg gtg ccc ccc     1248
Ala Ala Trp Ser Leu Pro Gly Leu Gly Gln Asp Thr Leu Val Pro Pro
        380                 385                 390

gtg tac act gtc agc cag gtg tgg cgg tca gat gtc cag ttt gcc tgg     1296
Val Tyr Thr Val Ser Gln Val Trp Arg Ser Asp Val Gln Phe Ala Trp
    395                 400                 405

aag cac ctc ttg tgt cca gat gtc tct tac aga cac ctg ggg ctc ttg     1344
Lys His Leu Leu Cys Pro Asp Val Ser Tyr Arg His Leu Gly Leu Leu
410                 415                 420                 425

atc ctg gca ctg ctg gcc ctc ctc acc cta ctg ggt gtt gtt ctg gcc     1392
Ile Leu Ala Leu Leu Ala Leu Leu Thr Leu Leu Gly Val Val Leu Ala
                430                 435                 440
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ctc acc tgc cgg cgc cca cag tca ggc ccg ggc cca gcg cgg cca gtg     1440
Leu Thr Cys Arg Arg Pro Gln Ser Gly Pro Gly Pro Ala Arg Pro Val
            445                 450                 455

ctc ctc ctg cac gcg gcg gac tcg gag gcg cag cgg cgc ctg gtg gga     1488
Leu Leu Leu His Ala Ala Asp Ser Glu Ala Gln Arg Arg Leu Val Gly
        460                 465                 470

gcg ctg gct gaa ctg cta cgg gca gcg ctg ggc ggc ggg cgc gac gtg     1536
Ala Leu Ala Glu Leu Leu Arg Ala Ala Leu Gly Gly Gly Arg Asp Val
    475                 480                 485

atc gtg gac ctg tgg gag ggg agg cac gtg gcg cgc gtg ggc ccg ctg     1584
Ile Val Asp Leu Trp Glu Gly Arg His Val Ala Arg Val Gly Pro Leu
490                 495                 500                 505

ccg tgg ctc tgg gcg gcg cgg acg cgc gta gcg cgg gag cag ggc act     1632
Pro Trp Leu Trp Ala Ala Arg Thr Arg Val Ala Arg Glu Gln Gly Thr
                510                 515                 520

gtg ctg ctg ctg tgg agc ggc gcc gac ctt cgc ccg gtc agc ggc ccc     1680
Val Leu Leu Leu Trp Ser Gly Ala Asp Leu Arg Pro Val Ser Gly Pro
            525                 530                 535

gac ccc cgc gcc gcg ccc ctg ctc gcc ctg ctc cac gct gcc ccg cgc     1728
Asp Pro Arg Ala Ala Pro Leu Leu Ala Leu Leu His Ala Ala Pro Arg
        540                 545                 550

ccg ctg ctg ctg ctc gct tac ttc agt cgc ctc tgc gcc aag ggc gac     1776
Pro Leu Leu Leu Leu Ala Tyr Phe Ser Arg Leu Cys Ala Lys Gly Asp
    555                 560                 565

atc ccc ccg ccg ctg cgc gcc ctg ccg cgc tac cgc ctg ctg cgc gac     1824
Ile Pro Pro Pro Leu Arg Ala Leu Pro Arg Tyr Arg Leu Leu Arg Asp
570                 575                 580                 585

ctg ccg cgt ctg ctg cgg gcg ctg gac gcg cgg cct ttc gca gag gcc     1872
Leu Pro Arg Leu Leu Arg Ala Leu Asp Ala Arg Pro Phe Ala Glu Ala
                590                 595                 600

acc agc tgg ggc cgc ctt ggg gcg cgg cag cgc agg cag agc cgc cta     1920
Thr Ser Trp Gly Arg Leu Gly Ala Arg Gln Arg Arg Gln Ser Arg Leu
            605                 610                 615

gag ctg tgc agc cgg ctc gaa cga gag gcc gcc cga ctt gca gac cta     1968
Glu Leu Cys Ser Arg Leu Glu Arg Glu Ala Ala Arg Leu Ala Asp Leu
        620                 625                 630

ggt tgagcagagc tccaccgcag tcccgggtgt ctgcggccgc t                   2012
Gly
```

<210> 17
<211> 657
<212> PRT
<213> Unknown

<400> 17

```
Met Gly Ser Ser Arg Leu Ala Ala Leu Leu Leu Pro Leu Leu Leu Ile
            -20                 -15                 -10
```

```
Val Ile Asp Leu Ser Asp Ser Ala Gly Ile Gly Phe Arg His Leu Pro
         -5              -1  1               5

His Trp Asn Thr Arg Cys Pro Leu Ala Ser His Thr Glu Val Leu Pro
 10                  15                  20                  25

Ile Ser Leu Ala Ala Pro Gly Gly Pro Ser Ser Pro Gln Ser Leu Gly
                 30                  35                  40

Val Cys Glu Ser Gly Thr Val Pro Ala Val Cys Ala Ser Ile Cys Cys
             45                  50                  55

Gln Val Ala Gln Val Phe Asn Gly Ala Ser Ser Thr Ser Trp Cys Arg
         60                  65                  70

Asn Pro Lys Ser Leu Pro His Ser Ser Ser Ile Gly Asp Thr Arg Cys
     75                  80                  85

Gln His Leu Leu Arg Gly Ser Cys Cys Leu Val Val Thr Cys Leu Arg
 90                  95                 100                 105

Arg Ala Ile Thr Phe Pro Ser Pro Pro Gln Thr Ser Pro Thr Arg Asp
                110                 115                 120

Phe Ala Leu Lys Gly Pro Asn Leu Arg Ile Gln Arg His Gly Lys Val
            125                 130                 135

Phe Pro Asp Trp Thr His Lys Gly Met Glu Val Gly Thr Gly Tyr Asn
        140                 145                 150

Arg Arg Trp Val Gln Leu Ser Gly Gly Pro Glu Phe Ser Phe Asp Leu
    155                 160                 165

Leu Pro Glu Ala Arg Ala Ile Arg Val Thr Ile Ser Ser Gly Pro Glu
170                 175                 180                 185

Val Ser Val Arg Leu Cys His Gln Trp Ala Leu Glu Cys Glu Glu Leu
                190                 195                 200

Ser Ser Pro Tyr Asp Val Gln Lys Ile Val Ser Gly Gly His Thr Val
            205                 210                 215

Glu Leu Pro Tyr Glu Phe Leu Leu Pro Cys Leu Cys Ile Glu Ala Ser
        220                 225                 230

Tyr Leu Gln Glu Asp Thr Val Arg Arg Lys Lys Cys Pro Phe Gln Ser
    235                 240                 245

Trp Pro Glu Ala Tyr Gly Ser Asp Phe Trp Lys Ser Val His Phe Thr
250                 255                 260                 265

Asp Tyr Ser Gln His Thr Gln Met Val Met Ala Leu Thr Leu Arg Cys
                270                 275                 280

Pro Leu Lys Leu Glu Ala Ala Leu Cys Gln Arg His Asp Trp His Thr
            285                 290                 295

Leu Cys Lys Asp Leu Pro Asn Ala Thr Ala Arg Glu Ser Asp Gly Trp
        300                 305                 310
```

```
Tyr Val Leu Glu Lys Val Asp Leu His Pro Gln Leu Cys Phe Lys Val
    315                 320                 325

Gln Pro Trp Phe Ser Phe Gly Asn Ser Ser His Val Glu Cys Pro His
330                 335                 340                     345

Gln Thr Gly Ser Leu Thr Ser Trp Asn Val Ser Met Asp Thr Gln Ala
                350                 355                 360

Gln Gln Leu Ile Leu His Phe Ser Ser Arg Met His Ala Thr Phe Ser
            365                 370                 375

Ala Ala Trp Ser Leu Pro Gly Leu Gly Gln Asp Thr Leu Val Pro Pro
        380                 385                 390

Val Tyr Thr Val Ser Gln Val Trp Arg Ser Asp Val Gln Phe Ala Trp
    395                 400                 405

Lys His Leu Leu Cys Pro Asp Val Ser Tyr Arg His Leu Gly Leu Leu
410                 415                 420                     425

Ile Leu Ala Leu Leu Ala Leu Leu Thr Leu Leu Gly Val Val Leu Ala
                430                 435                 440

Leu Thr Cys Arg Arg Pro Gln Ser Gly Pro Gly Pro Ala Arg Pro Val
            445                 450                 455

Leu Leu Leu His Ala Ala Asp Ser Glu Ala Gln Arg Arg Leu Val Gly
        460                 465                 470

Ala Leu Ala Glu Leu Leu Arg Ala Ala Leu Gly Gly Gly Arg Asp Val
    475                 480                 485

Ile Val Asp Leu Trp Glu Gly Arg His Val Ala Arg Val Gly Pro Leu
490                 495                 500                     505

Pro Trp Leu Trp Ala Ala Arg Thr Arg Val Ala Arg Glu Gln Gly Thr
                510                 515                 520

Val Leu Leu Leu Trp Ser Gly Ala Asp Leu Arg Pro Val Ser Gly Pro
            525                 530                 535

Asp Pro Arg Ala Ala Pro Leu Leu Ala Leu Leu His Ala Ala Pro Arg
        540                 545                 550

Pro Leu Leu Leu Leu Ala Tyr Phe Ser Arg Leu Cys Ala Lys Gly Asp
    555                 560                 565

Ile Pro Pro Pro Leu Arg Ala Leu Pro Arg Tyr Arg Leu Leu Arg Asp
570                 575                 580                     585

Leu Pro Arg Leu Leu Arg Ala Leu Asp Ala Arg Pro Phe Ala Glu Ala
                590                 595                 600

Thr Ser Trp Gly Arg Leu Gly Ala Arg Gln Arg Arg Gln Ser Arg Leu
            605                 610                 615

Glu Leu Cys Ser Arg Leu Glu Arg Glu Ala Ala Arg Leu Ala Asp Leu
        620                 625                 630
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Gly

<210> 18
<211> 1971
<212> DNA
<213> reverse translation

<220>
<221> misc_feature
<222> (1)..(1971)
<223> n may be a, c, g, or t

<400> 18
atgggnwsnw snmgnytngc ngcnytnytn ytnccnytny tnytnathgt nathgayytn 60

wsngaywsng cnggnathgg nttymgncay ytnccncayt ggaayacnmg ntgyccnytn 120

gcnwsncaya cngargtnyt nccnathwsn ytngcngcnc cnggnggncc nwsnwsnccn 180

carwsnytng gngtntgyga rwsnggnacn gtnccngcng tntgygcnws nathtgytgy 240

cargtngcnc argtnttyaa yggngcnwsn wsnacnwsnt ggtgymgnaa yccnaarwsn 300

ytnccncayw snwsnwsnat hggngayacn mgntgycarc ayytnytnmg nggnwsntgy 360

tgyytngtng tnacntgyyt nmgnmgngcn athacnttyc cnwsnccncc ncaracnwsn 420

ccnacnmgng ayttygcnyt naarggnccn aayytnmgna thcarmgnca yggnaargtn 480

ttyccngayt ggacncayaa rggnatggar gtnggnacng gntayaaymg nmgntgggtn 540

carytnwsng gnggnccnga rttywsntty gayytnytnc cngargcnmg ngcnathmgn 600

gtnacnathw snwsnggncc ngargtnwsn gtnmgnytnt gycaycartg ggcnytngar 660

tgygargary tnwsnwsncc ntaygaygtn caraarathg tnwsnggngg ncayacngtn 720

garytnccnt aygarttyyt nytnccntgy ytntgyathg argcnwsnta yytncargar 780

gayacngtnm gnmgnaaraa rtgyccntty carwsntggc cngargcnta yggnwsngay 840

ttytggaarw sngtncaytt yacngaytay wsncarcaya cncaratggt natggcnytn 900

acnytnmgnt gyccnytnaa rytngargcn gcnytntgyc armgncayga ytggcayacn 960

ytntgyaarg ayytnccnaa ygcnacngcn mgngarwsng ayggntggta ygtnytngar 1020

aargtngayy tncayccnca rytntgytty aargtncarc cntggttyws nttyggnaay 1080

wsnwsncayg tngartgycc ncaycaracn ggnwsnytna cnwsntggaa ygtnwsnatg 1140

gayacncarg cncarcaryt nathytncay ttywsnwsnm gnatgcaygc nacnttywsn 1200

gcngcntggw snytnccngg nytnggncar gayacnytng tnccnccngt ntayacngtn 1260

wsncargtnt ggmgnwsnga ygtncartty gcntggaarc ayytnytntg yccngaygtn 1320

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wsntaymgnc ayytnggnyt nytnathytn gcnytnytng cnytnytnac nytnytnggn 1380

gtngtnytng cnytnacntg ymgnmgnccn carwsnggnc cnggnccngc nmgnccngtn 1440

ytnytnytnc aygcngcnga ywsngargcn carmgnmgny tngtnggngc nytngcngar 1500

ytnytnmgng cngcnytngg nggnggnmgn gaygtnathg tngayytntg ggarggnmgn 1560

caygtngcnm gngtnggncc nytnccntgg ytntgggcng cnmgnacnmg ngtngcnmgn 1620

garcarggna cngtnytnyt nytntggwsn ggngcngayy tnmgnccngt nwsnggnccn 1680

gayccnmgng cngcnccnyt nytngcnytn ytncaygcng cnccnmgncc nytnytnytn 1740

ytngcntayt tywsnmgnyt ntgygcnaar ggngayathc cnccnccnyt nmgngcnytn 1800

ccnmgntaym gnytnytnmg ngayytnccn mgnytnytnm gngcnytnga ygcnmgnccn 1860

ttygcngarg cnacnwsntg gggnmgnytn ggngcnmgnc armgnmgnca rwsnmgnytn 1920

garytntgyw snmgnytnga rmgngargcn gcnmgnytng cngayytngg n          1971
```

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<210> 19
<211> 808
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:rodent; surmised
      Mus musculus

<220>
<221> CDS
<222> (78)..(806)

<220>
<221> mat_peptide
<222> (147)..(806)

<400> 19
cagctccggg ccaggccctg ctgccctctt gcagacagga aagacatggt ctctgcgccc 60

tgatcctaca gaagctc atg ggg agc ccc aga ctg gca gcc ttg ctc ctg    110
                   Met Gly Ser Pro Arg Leu Ala Ala Leu Leu Leu
                                   -20                 -15

tct ctc ccg cta ctg ctc atc ggc ctc gct gtg tct gct cgg gtt gcc   158
Ser Leu Pro Leu Leu Leu Ile Gly Leu Ala Val Ser Ala Arg Val Ala
        -10                 -5                  -1   1

tgc ccc tgc ctg cgg agt tgg acc agc cac tgt ctc ctg gcc tac cgt   206
Cys Pro Cys Leu Arg Ser Trp Thr Ser His Cys Leu Leu Ala Tyr Arg
  5                 10                  15                  20

gtg gat aaa cgt ttt gct ggc ctt cag tgg ggc tgg ttc cct ctc ttg   254
Val Asp Lys Arg Phe Ala Gly Leu Gln Trp Gly Trp Phe Pro Leu Leu
                25                  30                  35

gtg agg aaa tct aaa agt cct cct aaa ttt gaa gac tat tgg agg cac   302
```

```
Val Arg Lys Ser Lys Ser Pro Pro Lys Phe Glu Asp Tyr Trp Arg His
            40                  45                  50

agg aca cca gca tcc ttc cag agg aag ctg cta ggc agc cct tcc ctg    350
Arg Thr Pro Ala Ser Phe Gln Arg Lys Leu Leu Gly Ser Pro Ser Leu
        55                  60                  65

tct gag gaa agc cat cga att tcc atc ccc tcc tca gcc atc tcc cac    398
Ser Glu Glu Ser His Arg Ile Ser Ile Pro Ser Ser Ala Ile Ser His
    70                  75                  80

aga ggc caa cgc acc aaa agg gcc cag cct tca gct gca gaa gga aga    446
Arg Gly Gln Arg Thr Lys Arg Ala Gln Pro Ser Ala Ala Glu Gly Arg
85                  90                  95                  100

gaa cat ctc cct gaa gca ggg tca caa aag tgt gga gga cct gaa ttc    494
Glu His Leu Pro Glu Ala Gly Ser Gln Lys Cys Gly Gly Pro Glu Phe
                105                 110                 115

tcc ttt gat ttg ctg ccc gag gtg cag gct gtt cgg gtg act att cct    542
Ser Phe Asp Leu Leu Pro Glu Val Gln Ala Val Arg Val Thr Ile Pro
            120                 125                 130

gca ggc ccc aag gca cgt gtg cgc ctt tgt tat cag tgg gca ctg gaa    590
Ala Gly Pro Lys Ala Arg Val Arg Leu Cys Tyr Gln Trp Ala Leu Glu
        135                 140                 145

tgt gaa gac ttg agt agc cct ttt gat acc cag aaa att gtg tct gga    638
Cys Glu Asp Leu Ser Ser Pro Phe Asp Thr Gln Lys Ile Val Ser Gly
    150                 155                 160

ggg cac act gta gac ctg cct tat gaa ttc ctt ctg ccc tgc atg tgc    686
Gly His Thr Val Asp Leu Pro Tyr Glu Phe Leu Leu Pro Cys Met Cys
165                 170                 175                 180

ata gag gcc tcc tac ctg caa gag gac act gtg agg cgc aaa agt gtc    734
Ile Glu Ala Ser Tyr Leu Gln Glu Asp Thr Val Arg Arg Lys Ser Val
                185                 190                 195

cct tcc aga gct ggc ctg aag ctt atg gct cag act tct ggc agt caa    782
Pro Ser Arg Ala Gly Leu Lys Leu Met Ala Gln Thr Ser Gly Ser Gln
            200                 205                 210

tac gct tca ctg act aca gcc agc ac                                 808
Tyr Ala Ser Leu Thr Thr Ala Ser
        215                 220


<210> 20
<211> 243
<212> PRT
<213> Unknown

<400> 20
Met Gly Ser Pro Arg Leu Ala Ala Leu Leu Leu Ser Leu Pro Leu Leu
            -20                 -15                 -10

Leu Ile Gly Leu Ala Val Ser Ala Arg Val Ala Cys Pro Cys Leu Arg
        -5                  -1   1               5
```

Ser Trp Thr Ser His Cys Leu Leu Ala Tyr Arg Val Asp Lys Arg Phe
10 15 20 25

Ala Gly Leu Gln Trp Gly Trp Phe Pro Leu Leu Val Arg Lys Ser Lys
30 35 40

Ser Pro Pro Lys Phe Glu Asp Tyr Trp Arg His Arg Thr Pro Ala Ser
45 50 55

Phe Gln Arg Lys Leu Leu Gly Ser Pro Ser Leu Ser Glu Glu Ser His
60 65 70

Arg Ile Ser Ile Pro Ser Ser Ala Ile Ser His Arg Gly Gln Arg Thr
75 80 85

Lys Arg Ala Gln Pro Ser Ala Ala Glu Gly Arg Glu His Leu Pro Glu
90 95 100 105

Ala Gly Ser Gln Lys Cys Gly Gly Pro Glu Phe Ser Phe Asp Leu Leu
110 115 120

Pro Glu Val Gln Ala Val Arg Val Thr Ile Pro Ala Gly Pro Lys Ala
125 130 135

Arg Val Arg Leu Cys Tyr Gln Trp Ala Leu Glu Cys Glu Asp Leu Ser
140 145 150

Ser Pro Phe Asp Thr Gln Lys Ile Val Ser Gly Gly His Thr Val Asp
155 160 165

Leu Pro Tyr Glu Phe Leu Leu Pro Cys Met Cys Ile Glu Ala Ser Tyr
170 175 180 185

Leu Gln Glu Asp Thr Val Arg Arg Lys Ser Val Pro Ser Arg Ala Gly
190 195 200

Leu Lys Leu Met Ala Gln Thr Ser Gly Ser Gln Tyr Ala Ser Leu Thr
205 210 215

Thr Ala Ser
220

<210> 21
<211> 729
<212> DNA
<213> reverse translation

<220>
<221> misc_feature
<222> (1)..(729)
<223> n may be a, c, g, or t

<400> 21
atgggnwsnc cnmgnytngc ngcnytnytn ytnwsnytnc cnytnytnyt nathggnytn 60

gcngtnwsng cnmgngtngc ntgyccntgy ytnmgnwsnt ggacnwsnca ytgyytnytn 120

gcntaymgng tngayaarmg nttygcnggn ytncartggg gntggttycc nytnytngtn 180

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mgnaarwsna arwsnccncc naarttygar gaytaytggm gncaymgnac nccngcnwsn 240

ttycarmgna arytnytngg nwsnccnwsn ytnwsngarg arwsncaymg nathwsnath 300

ccnwsnwsng cnathwsnca ymgnggncar mgnacnaarm gngcncarcc nwsngcngcn 360

garggnmgng arcayytncc ngargcnggn wsncaraart gyggnggncc ngarttywsn 420

ttygayytny tnccngargt ncargcngtn mgngtnacna thccngcngg nccnaargcn 480

mgngtnmgny tntgytayca rtgggcnytn gartgygarg ayytnwsnws nccnttygay 540

acncaraara thgtnwsngg nggncayacn gtngayytnc cntaygartt yytnytnccn 600

tgyatgtgya thgargcnws ntayytncar gargayacng tnmgnmgnaa rwsngtnccn 660

wsnmgngcng gnytnaaryt natggcncar acnwsnggnw sncartaygc nwsnytnacn 720

acngcnwsn                                                         729


<210> 22
<211> 2377
<212> DNA
<213> Unknown

<220>
<223> Description of Unknown Organism:primate; surmised
      Homo sapiens

<220>
<221> CDS
<222> (180)..(1874)

<400> 22
ttttgagcag aggcttccta ggctccgtag aaatttgcat acagcttcca cttcctgctt 60

cagagcctgt tcttctactt acctgggccc ggagaaggtg gagggagacg agaagccgcc 120

gagagccgac taccctccgg gcccagtctg tctgtccgtg gtggatctaa gaaactaga  179

atg aac cga agc att cct gtg gag gtt gat gaa tca gaa cca tac cca   227
Met Asn Arg Ser Ile Pro Val Glu Val Asp Glu Ser Glu Pro Tyr Pro
  1               5                  10                  15

agt cag ttg ctg aaa cca atc cca gaa tat tcc ccg gaa gag gaa tca   275
Ser Gln Leu Leu Lys Pro Ile Pro Glu Tyr Ser Pro Glu Glu Glu Ser
             20                  25                  30

gaa cca cct gct cca aat ata agg aac atg gca ccc aac agc ttg tct   323
Glu Pro Pro Ala Pro Asn Ile Arg Asn Met Ala Pro Asn Ser Leu Ser
         35                  40                  45

gca ccc aca atg ctt cac aat tcc tcc gga gac ttt tct caa gct cac   371
Ala Pro Thr Met Leu His Asn Ser Ser Gly Asp Phe Ser Gln Ala His
     50                  55                  60

tca acc ctg aaa ctt gca aat cac cag cgg cct gta tcc cgg cag gtc   419
Ser Thr Leu Lys Leu Ala Asn His Gln Arg Pro Val Ser Arg Gln Val
 65                  70                  75                  80
```

```
acc tgc ctg cgc act caa gtt ctg gag gac agt gaa gac agt ttc tgc     467
Thr Cys Leu Arg Thr Gln Val Leu Glu Asp Ser Glu Asp Ser Phe Cys
                85                  90                  95

agg aga cac cca ggc ctg ggc aaa gct ttc cct tct ggg tgc tct gca     515
Arg Arg His Pro Gly Leu Gly Lys Ala Phe Pro Ser Gly Cys Ser Ala
            100                 105                 110

gtc agc gag cct gcg tct gag tct gtg gtt gga gcc ctc cct gca gag     563
Val Ser Glu Pro Ala Ser Glu Ser Val Val Gly Ala Leu Pro Ala Glu
        115                 120                 125

cat cag ttt tca ttt atg gaa aaa cgt aat caa tgg ctg gta tct cag     611
His Gln Phe Ser Phe Met Glu Lys Arg Asn Gln Trp Leu Val Ser Gln
    130                 135                 140

ctt tca gcg gct tct cct gac act ggc cat gac tca gac aaa tca gac     659
Leu Ser Ala Ala Ser Pro Asp Thr Gly His Asp Ser Asp Lys Ser Asp
145                 150                 155                 160

caa agt tta cct aat gcc tca gca gac tcc ttg ggc ggt agc cag gag     707
Gln Ser Leu Pro Asn Ala Ser Ala Asp Ser Leu Gly Gly Ser Gln Glu
                165                 170                 175

atg gtg caa cgg ccc cag cct cac agg aac cga gca ggc ctg gat ctg     755
Met Val Gln Arg Pro Gln Pro His Arg Asn Arg Ala Gly Leu Asp Leu
            180                 185                 190

cca acc ata gac acg gga tat gat tcc cag ccc cag gat gtc ctg ggc     803
Pro Thr Ile Asp Thr Gly Tyr Asp Ser Gln Pro Gln Asp Val Leu Gly
        195                 200                 205

atc agg cag ctg gaa agg ccc ctg ccc ctc acc tcc gtg tgt tac ccc     851
Ile Arg Gln Leu Glu Arg Pro Leu Pro Leu Thr Ser Val Cys Tyr Pro
    210                 215                 220

cag gac ctc ccc aga cct ctc agg tcc agg gag ttc cct cag ttt gaa     899
Gln Asp Leu Pro Arg Pro Leu Arg Ser Arg Glu Phe Pro Gln Phe Glu
225                 230                 235                 240

cct cag agg tat cca gca tgt gca cag atg ctg cct ccc aat ctt tcc     947
Pro Gln Arg Tyr Pro Ala Cys Ala Gln Met Leu Pro Pro Asn Leu Ser
                245                 250                 255

cca cat gct cca tgg aac tat cat tac cat tgt cct gga agt ccc gat     995
Pro His Ala Pro Trp Asn Tyr His Tyr His Cys Pro Gly Ser Pro Asp
            260                 265                 270

cac cag gtg cca tat ggc cat gac tac cct cga gca gcc tac cag caa     1043
His Gln Val Pro Tyr Gly His Asp Tyr Pro Arg Ala Ala Tyr Gln Gln
        275                 280                 285

gtg atc cag ccg gct ctg cct ggg cag ccc ctg cct gga gcc agt gtg     1091
Val Ile Gln Pro Ala Leu Pro Gly Gln Pro Leu Pro Gly Ala Ser Val
    290                 295                 300

aga ggc ctg cac cct gtg cag aag gtt atc ctg aat tat ccc agc ccc     1139
Arg Gly Leu His Pro Val Gln Lys Val Ile Leu Asn Tyr Pro Ser Pro
305                 310                 315                 320
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tgg gac caa gaa gag agg ccc gca cag aga gac tgc tcc ttt ccg ggg    1187
Trp Asp Gln Glu Glu Arg Pro Ala Gln Arg Asp Cys Ser Phe Pro Gly
                325                 330                 335

ctt cca agg cac cag gac cag cca cat cac cag cca cct aat aga gct    1235
Leu Pro Arg His Gln Asp Gln Pro His His Gln Pro Pro Asn Arg Ala
            340                 345                 350

ggt gct cct ggg gag tcc ttg gag tgc cct gca gag ctg aga cca cag    1283
Gly Ala Pro Gly Glu Ser Leu Glu Cys Pro Ala Glu Leu Arg Pro Gln
        355                 360                 365

gtt ccc cag cct ccg tcc cca gct gct gtg cct aga ccc cct agc aac    1331
Val Pro Gln Pro Pro Ser Pro Ala Ala Val Pro Arg Pro Pro Ser Asn
    370                 375                 380

cct cca gcc aga gga act cta aaa aca agc aat ttg cca gaa gaa ttg    1379
Pro Pro Ala Arg Gly Thr Leu Lys Thr Ser Asn Leu Pro Glu Glu Leu
385                 390                 395                 400

cgg aaa gtc ttt atc act tat tcg atg gac aca gct atg gag gtg gtg    1427
Arg Lys Val Phe Ile Thr Tyr Ser Met Asp Thr Ala Met Glu Val Val
                405                 410                 415

aaa ttc gtg aac ttt ttg ttg gta aat ggc ttc caa act gca att gac    1475
Lys Phe Val Asn Phe Leu Leu Val Asn Gly Phe Gln Thr Ala Ile Asp
            420                 425                 430

ata ttt gag gat aga atc cga ggc att gat atc att aaa tgg atg gag    1523
Ile Phe Glu Asp Arg Ile Arg Gly Ile Asp Ile Ile Lys Trp Met Glu
        435                 440                 445

cgc tac ctt agg gat aag acc gtg atg ata atc gta gca atc agc ccc    1571
Arg Tyr Leu Arg Asp Lys Thr Val Met Ile Ile Val Ala Ile Ser Pro
    450                 455                 460

aaa tac aaa cag gac gtg gaa ggc gct gag tcg cag ctg gac gag gat    1619
Lys Tyr Lys Gln Asp Val Glu Gly Ala Glu Ser Gln Leu Asp Glu Asp
465                 470                 475                 480

gag cat ggc tta cat act aag tac att cat cga atg atg cag att gag    1667
Glu His Gly Leu His Thr Lys Tyr Ile His Arg Met Met Gln Ile Glu
                485                 490                 495

ttc ata aaa caa gga agc atg aat ttc aga ttc atc cct gtg ctc ttc    1715
Phe Ile Lys Gln Gly Ser Met Asn Phe Arg Phe Ile Pro Val Leu Phe
            500                 505                 510

cca aat gct aag aag gag cat gtg ccc acc tgg ctt cag aac act cat    1763
Pro Asn Ala Lys Lys Glu His Val Pro Thr Trp Leu Gln Asn Thr His
        515                 520                 525

gtc tac agc tgg ccc aag aat aaa aaa aac atc ctg ctg cgg ctg ctg    1811
Val Tyr Ser Trp Pro Lys Asn Lys Lys Asn Ile Leu Leu Arg Leu Leu
    530                 535                 540

aga gag gaa gag tat gtg gct cct cca cgg ggg cct ctg ccc acc ctt    1859
Arg Glu Glu Glu Tyr Val Ala Pro Pro Arg Gly Pro Leu Pro Thr Leu
545                 550                 555                 560
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cag gtg gtt ccc ttg tgacaccgtt catccccaga tcactgaggc caggccatgt   1914
Gln Val Val Pro Leu
                565

ttggggcctt gttctgacag cattctggct gaggctggtc ggtagcactc ctggctggtt 1974

tttttctgtt cctccccgag aggccctctg gcccccagga aacctgttgt gcagagctct 2034

tccccggaga cctccacaca ccctggcttt gaagtggagt ctgtgactgc tctgcattct 2094

ctgcttttaa aaaaaccatt gcaggtgcca gtgtcccata tgttcctcct gacagtttga 2154

tgtgtccatt ctgggcctct cagtgcttag caagtagata atgtaaggga tgtggcagca 2214

aatggaaatg actacaaaca ctctcctatc aatcacttca ggctactttt atgagttagc 2274

cagatgcttg tgtatcctca gaccaaactg attcatgtac aaataataaa atgtttactc 2334

ttttgtaaaa aaaaaaaaaa aaaaaaaaag aaaaaaaaaa aaa                   2377


<210> 23
<211> 565
<212> PRT
<213> Unknown

<400> 23
Met Asn Arg Ser Ile Pro Val Glu Val Asp Glu Ser Glu Pro Tyr Pro
1               5                   10                  15

Ser Gln Leu Leu Lys Pro Ile Pro Glu Tyr Ser Pro Glu Glu Glu Ser
            20                  25                  30

Glu Pro Pro Ala Pro Asn Ile Arg Asn Met Ala Pro Asn Ser Leu Ser
        35                  40                  45

Ala Pro Thr Met Leu His Asn Ser Ser Gly Asp Phe Ser Gln Ala His
    50                  55                  60

Ser Thr Leu Lys Leu Ala Asn His Gln Arg Pro Val Ser Arg Gln Val
65                  70                  75                  80

Thr Cys Leu Arg Thr Gln Val Leu Glu Asp Ser Glu Asp Ser Phe Cys
                85                  90                  95

Arg Arg His Pro Gly Leu Gly Lys Ala Phe Pro Ser Gly Cys Ser Ala
            100                 105                 110

Val Ser Glu Pro Ala Ser Glu Ser Val Val Gly Ala Leu Pro Ala Glu
        115                 120                 125

His Gln Phe Ser Phe Met Glu Lys Arg Asn Gln Trp Leu Val Ser Gln
    130                 135                 140

Leu Ser Ala Ala Ser Pro Asp Thr Gly His Asp Ser Asp Lys Ser Asp
145                 150                 155                 160

Gln Ser Leu Pro Asn Ala Ser Ala Asp Ser Leu Gly Gly Ser Gln Glu
                165                 170                 175
```

```
Met Val Gln Arg Pro Gln Pro His Arg Asn Arg Ala Gly Leu Asp Leu
            180                 185                 190

Pro Thr Ile Asp Thr Gly Tyr Asp Ser Gln Pro Gln Asp Val Leu Gly
        195                 200                 205

Ile Arg Gln Leu Glu Arg Pro Leu Pro Leu Thr Ser Val Cys Tyr Pro
    210                 215                 220

Gln Asp Leu Pro Arg Pro Leu Arg Ser Arg Glu Phe Pro Gln Phe Glu
225                 230                 235                 240

Pro Gln Arg Tyr Pro Ala Cys Ala Gln Met Leu Pro Pro Asn Leu Ser
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Pro His Ala Pro Trp Asn Tyr His Tyr His Cys Pro Gly Ser Pro Asp
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His Gln Val Pro Tyr Gly His Asp Tyr Pro Arg Ala Ala Tyr Gln Gln
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305                 310                 315                 320

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385                 390                 395                 400

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Lys Phe Val Asn Phe Leu Leu Val Asn Gly Phe Gln Thr Ala Ile Asp
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Ile Phe Glu Asp Arg Ile Arg Gly Ile Asp Ile Ile Lys Trp Met Glu
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Arg Tyr Leu Arg Asp Lys Thr Val Met Ile Ile Val Ala Ile Ser Pro
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Lys Tyr Lys Gln Asp Val Glu Gly Ala Glu Ser Gln Leu Asp Glu Asp
465                 470                 475                 480

Glu His Gly Leu His Thr Lys Tyr Ile His Arg Met Met Gln Ile Glu
                485                 490                 495
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515 520 525

Val Tyr Ser Trp Pro Lys Asn Lys Lys Asn Ile Leu Leu Arg Leu Leu
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aayatggcnc cnaaywsnyt nwsngcnccn acnatgytnc ayaaywsnws nggngaytty 180

wsncargcnc aywsnacnyt naarytngcn aaycaycarm gnccngtnws nmgncargtn 240

acntgyytnm gnacncargt nytngargay wsngargayw snttytgymg nmgncayccn 300

ggnytnggna argcnttycc nwsnggntgy wsngcngtnw sngarccngc nwsngarwsn 360

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ytngtnwsnc arytnwsngc ngcnwsnccn gayacnggnc aygaywsnga yaarwsngay 480

carwsnytnc cnaaygcnws ngcngaywsn ytnggnggnw sncargarat ggtncarmgn 540

ccncarccnc aymgnaaymg ngcnggnytn gayytnccna cnathgayac nggntaygay 600

wsncarccnc argaygtnyt nggnathmgn carytngarm gnccnytncc nytnacnwsn 660

gtntgytayc cncargayyt nccnmgnccn ytnmgnwsnm gngarttycc ncarttygar 720

ccncarmgnt ayccngcntg ygcncaratg ytnccnccna ayytnwsncc ncaygcnccn 780

tggaaytayc aytaycaytg yccnggnwsn ccngaycayc argtnccnta yggncaygay 840

tayccnmgng cngcntayca rcargtnath carccngcny tnccnggnca rccnytnccn 900

ggngcnwsng tnmgnggnyt ncayccngtn caraargtna thytnaayta yccnwsnccn 960

tgggaycarg argarmgncc ngcncarmgn gaytgywsnt tyccnggnyt nccnmgncay 1020

cargaycarc cncaycayca rccnccnaay mgngcnggng cnccnggnga rwsnytngar 1080

tgyccngcng arytnmgncc ncargtnccn carccnccnw snccngcngc ngtnccnmgn 1140

ccnccnwsna ayccnccngc nmgnggnacn ytnaaracnw snaayytncc ngargarytn 1200

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ttyytnytng tnaayggntt ycaracngcn athgayatht tygargaymg nathmgnggn 1320

athgayatha thaartggat ggarmgntay ytnmgngaya aracngtnat gathathgtn 1380

gcnathwsnc cnaartayaa rcargaygtn garggngcng arwsncaryt ngaygargay 1440

garcayggny tncayacnaa rtayathcay mgnatgatgc arathgartt yathaarcar 1500

ggnwsnatga ayttymgntt yathccngtn ytnttyccna aygcnaaraa rgarcaygtn 1560

ccnacntggy tncaraayac ncaygtntay wsntggccna araayaaraa raayathytn 1620

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gaa ctt gag agg tat cca atg aac gcc cag ctg ctg ccg ccc cat cct     96
Glu Leu Glu Arg Tyr Pro Met Asn Ala Gln Leu Leu Pro Pro His Pro
             20                  25                  30

tcc cca cag gcc cca tgg aac tgt cag tac tac tgc ccc gga ggg ccc    144
Ser Pro Gln Ala Pro Trp Asn Cys Gln Tyr Tyr Cys Pro Gly Gly Pro
         35                  40                  45

tac cac cac cag gtg cca cac ggc cat ggc tac cct cca gca gca gcc    192
Tyr His His Gln Val Pro His Gly His Gly Tyr Pro Pro Ala Ala Ala
     50                  55                  60

tac cag caa gta ctc cag cct gct ctg cct ggg cag gtc ctt cct ggg    240
Tyr Gln Gln Val Leu Gln Pro Ala Leu Pro Gly Gln Val Leu Pro Gly
 65                  70                  75                  80
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gca agg gca aga ggc cca cgc cct gtg cag aag gtc atc ctg aat gac 288
Ala Arg Ala Arg Gly Pro Arg Pro Val Gln Lys Val Ile Leu Asn Asp
85 90 95

tcc agc ccc caa gac caa gaa gag aga cct gca cag aga gac ttc tct 336
Ser Ser Pro Gln Asp Gln Glu Glu Arg Pro Ala Gln Arg Asp Phe Ser
100 105 110

ttc ccg agg ctc ccg agg gac cag ctc tac cgc cca cca tct aat gga 384
Phe Pro Arg Leu Pro Arg Asp Gln Leu Tyr Arg Pro Pro Ser Asn Gly
115 120 125

gtg gaa gcc cct gag gag tcc ttg gac ctt cct gca gag ctg aga cca 432
Val Glu Ala Pro Glu Glu Ser Leu Asp Leu Pro Ala Glu Leu Arg Pro
130 135 140

cat ggt ccc cag gct cca tcc cta gct gcc gtg cct aga ccc cct agc 480
His Gly Pro Gln Ala Pro Ser Leu Ala Ala Val Pro Arg Pro Pro Ser
145 150 155 160

aac ccc tta gcc cga gga act cta aga acc agc aat ttg cca gaa gaa 528
Asn Pro Leu Ala Arg Gly Thr Leu Arg Thr Ser Asn Leu Pro Glu Glu
165 170 175

tta cgg aaa gtc ttt atc act tat tct atg gac aca gcc atg gag gtg 576
Leu Arg Lys Val Phe Ile Thr Tyr Ser Met Asp Thr Ala Met Glu Val
180 185 190

gtg aaa ttt gtg aac ttt ctg ttg gtg aac ggc ttc caa act gcg att 624
Val Lys Phe Val Asn Phe Leu Leu Val Asn Gly Phe Gln Thr Ala Ile
195 200 205

gac ata ttt gag gat aga atc cgg ggt att gat atc att aaa tgg atg 672
Asp Ile Phe Glu Asp Arg Ile Arg Gly Ile Asp Ile Ile Lys Trp Met
210 215 220

gag cgc tat ctt cga gat aag aca gtg atg ata atc gta gca atc agc 720
Glu Arg Tyr Leu Arg Asp Lys Thr Val Met Ile Ile Val Ala Ile Ser
225 230 235 240

ccc aaa tac aaa cag gat gtg gaa ggc gct gag tcg cag ctg gac gag 768
Pro Lys Tyr Lys Gln Asp Val Glu Gly Ala Glu Ser Gln Leu Asp Glu
245 250 255

gac gag cat ggc tta cat act aag tac att cat cgg atg atg cag att 816
Asp Glu His Gly Leu His Thr Lys Tyr Ile His Arg Met Met Gln Ile
260 265 270

gag ttc ata agt cag gga agc atg aac ttc aga ttc atc cct gtg ctc 864
Glu Phe Ile Ser Gln Gly Ser Met Asn Phe Arg Phe Ile Pro Val Leu
275 280 285

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Phe Pro Asn Ala Lys Lys Glu His Val Pro Thr Trp Leu Gln Asn Thr
290 295 300

cat gtt tac agc tgg ccc aag aat aag aaa aac atc ctg ctg cgg ctg 960
His Val Tyr Ser Trp Pro Lys Asn Lys Lys Asn Ile Leu Leu Arg Leu
305 310 315 320

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ctc agg gag gaa gag tat gtg gct cct ccc cga ggc cct ctg ccc acc    1008
Leu Arg Glu Glu Glu Tyr Val Ala Pro Pro Arg Gly Pro Leu Pro Thr
                325                 330                 335

ctt cag gtg gta ccc ttg tgacgatggc cactccagct cagtgccagc          1056
Leu Gln Val Val Pro Leu
            340

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cttctacaga gtcctctgtc tcctgagtct gagttgtcct cgctgggctt ccagagcttc 1176

agtgcctgga tgctgcaggt gacagaaaca aacatctatg accacaaaaa ctctcatcac 1236

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<212> PRT
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Glu Leu Glu Arg Tyr Pro Met Asn Ala Gln Leu Leu Pro Pro His Pro
            20                  25                  30

Ser Pro Gln Ala Pro Trp Asn Cys Gln Tyr Tyr Cys Pro Gly Gly Pro
        35                  40                  45

Tyr His His Gln Val Pro His Gly His Gly Tyr Pro Pro Ala Ala Ala
    50                  55                  60

Tyr Gln Gln Val Leu Gln Pro Ala Leu Pro Gly Gln Val Leu Pro Gly
 65                  70                  75                  80

Ala Arg Ala Arg Gly Pro Arg Pro Val Gln Lys Val Ile Leu Asn Asp
                 85                  90                  95

Ser Ser Pro Gln Asp Gln Glu Glu Arg Pro Ala Gln Arg Asp Phe Ser
            100                 105                 110

Phe Pro Arg Leu Pro Arg Asp Gln Leu Tyr Arg Pro Pro Ser Asn Gly
        115                 120                 125

Val Glu Ala Pro Glu Glu Ser Leu Asp Leu Pro Ala Glu Leu Arg Pro
    130                 135                 140

His Gly Pro Gln Ala Pro Ser Leu Ala Ala Val Pro Arg Pro Pro Ser
145                 150                 155                 160

Asn Pro Leu Ala Arg Gly Thr Leu Arg Thr Ser Asn Leu Pro Glu Glu
                165                 170                 175

Leu Arg Lys Val Phe Ile Thr Tyr Ser Met Asp Thr Ala Met Glu Val
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180 185 190

Val Lys Phe Val Asn Phe Leu Leu Val Asn Gly Phe Gln Thr Ala Ile
195 200 205

Asp Ile Phe Glu Asp Arg Ile Arg Gly Ile Asp Ile Ile Lys Trp Met
210 215 220

Glu Arg Tyr Leu Arg Asp Lys Thr Val Met Ile Ile Val Ala Ile Ser
225 230 235 240

Pro Lys Tyr Lys Gln Asp Val Glu Gly Ala Glu Ser Gln Leu Asp Glu
245 250 255

Asp Glu His Gly Leu His Thr Lys Tyr Ile His Arg Met Met Gln Ile
260 265 270

Glu Phe Ile Ser Gln Gly Ser Met Asn Phe Arg Phe Ile Pro Val Leu
275 280 285

Phe Pro Asn Ala Lys Lys Glu His Val Pro Thr Trp Leu Gln Asn Thr
290 295 300

His Val Tyr Ser Trp Pro Lys Asn Lys Lys Asn Ile Leu Leu Arg Leu
305 310 315 320

Leu Arg Glu Glu Glu Tyr Val Ala Pro Pro Arg Gly Pro Leu Pro Thr
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Leu Gln Val Val Pro Leu
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<212> DNA
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cartaytayt gyccnggngg nccntaycay caycargtnc cncayggnca yggntayccn 180

ccngcngcng cntaycarca rgtnytncar ccngcnytnc cnggncargt nytnccnggn 240

gcnmgngcnm gnggnccnmg nccngtncar aargtnathy tnaaygayws nwsnccncar 300

gaycargarg armgnccngc ncarmgngay ttywsnttyc cnmgnytncc nmgngaycar 360

ytntaymgnc cnccnwsnaa yggngtngar gcnccngarg arwsnytnga yytnccngcn 420

garytnmgnc cncayggncc ncargcnccn wsnytngcng cngtnccnmg nccnccnwsn 480

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gtnaayggnt tycaracngc nathgayath ttygargaym gnathmgngg nathgayath 660
athaartgga tggarmgnta yytnmgngay aaracngtna tgathathgt ngcnathwsn 720
ccnaartaya arcargaygt ngarggngcn garwsncary tngaygarga ygarcayggn 780
ytncayacna artayathca ymgnatgatg carathgart tyathwsnca rggnwsnatg 840
aayttymgnt tyathccngt nytnttyccn aaygcnaara argarcaygt nccnacntgg 900
ytncaraaya cncaygtnta ywsntggccn aaraayaara araayathyt nytnmgnytn 960
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ccnytn                                                            1026
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<211> 207
<212> PRT
<213> Unknown

<220>
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Val Ala Leu Asp Leu Leu Glu Glu Gln Ala Ile Ser Glu Ala Gly Val
         35                  40                  45

Met Thr Trp Val Gly Arg Gln Lys Gln Glu Met Val Glu Ser Asn Ser
     50                  55                  60

Lys Ile Ile Val Leu Cys Ser Arg Gly Thr Arg Ala Lys Trp Gln Ala
 65                  70                  75                  80

Leu Leu Gly Arg Gly Ala Pro Val Arg Leu Arg Cys Asp His Gly Lys
                 85                  90                  95

Pro Val Gly Asp Leu Phe Thr Ala Ala Met Asn Met Ile Leu Pro Asp
            100                 105                 110

Phe Lys Arg Pro Ala Cys Phe Gly Thr Tyr Val Val Cys Tyr Phe Ser
        115                 120                 125

Glu Val Ser Cys Asp Gly Asp Val Pro Asp Leu Phe Gly Ala Ala Pro
    130                 135                 140

Arg Tyr Pro Leu Met Asp Arg Phe Glu Glu Val Tyr Phe Arg Ile Gln
145                 150                 155                 160
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Asp Leu Glu Met Phe Gln Pro Gly Arg Met His Arg Val Gly Glu Leu
                165                 170                 175

Ser Gly Asp Asn Tyr Leu Arg Ser Pro Gly Gly Arg Gln Leu Arg Ala
            180                 185                 190

Ala Leu Asp Arg Phe Arg Asp Trp Gln Val Arg Cys Pro Asp Trp
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<210> 29
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<212> PRT
<213> Unknown

<220>
<223> Description of Unknown Organism:rodent; surmised
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Val Val Leu Lys Phe Ala Gln Phe Leu Ile Thr Ala Cys Gly Thr Glu
             20                  25                  30

Val Ala Leu Asp Leu Leu Glu Glu Gln Val Ile Ser Glu Val Gly Val
         35                  40                  45

Met Thr Trp Val Ser Arg Gln Lys Gln Glu Met Val Glu Ser Asn Ser
     50                  55                  60

Lys Ile Ile Ile Leu Cys Ser Arg Gly Thr Gln Ala Lys Trp Lys Ala
 65                  70                  75                  80

Ile Leu Gly Trp Ala Glu Pro Ala Val Gln Leu Arg Cys Asp His Trp
                 85                  90                  95

Lys Pro Ala Gly Asp Leu Phe Thr Ala Ala Met Asn Met Ile Leu Pro
            100                 105                 110

Asp Phe Lys Arg Pro Ala Cys Phe Gly Thr Tyr Val Val Cys Tyr Phe
        115                 120                 125

Ser Gly Ile Cys Ser Glu Arg Asp Val Pro Asp Leu Phe Asn Ile Thr
    130                 135                 140

Ser Arg Tyr Pro Leu Met Asp Arg Phe Glu Glu Val Tyr Phe Arg Ile
145                 150                 155                 160

Gln Asp Leu Glu Met Phe Glu Pro Gly Arg Met His His Val Arg Glu
                165                 170                 175

Leu Thr Gly Asp Asn Tyr Leu Gln Ser Pro Ser Gly Arg Gln Leu Lys
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Glu Ala Val Leu Arg Phe Gln Glu Trp Gln Thr Gln Cys Pro Asp Trp
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<212> PRT
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<220>
<223> Description of Unknown Organism:worm; surmised
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Cys Val Lys Lys Leu Val Glu Asn Leu Arg Asn Cys Ala Ser Cys Asp
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Pro Val Phe Asp Leu Glu Lys Leu Ile Thr Ala Glu Ile Val Pro Ser
35 40 45

Arg Trp Leu Val Asp Gln Ile Ser Ser Leu Lys Lys Phe Ile Ile Val
50 55 60

Val Ser Asp Cys Ala Glu Lys Ile Leu Asp Thr Glu Ala Ser Glu Thr
65 70 75 80

His Gln Leu Val Gln Ala Arg Pro Phe Ala Asp Leu Phe Gly Pro Ala
85 90 95

Met Glu Met Ile Ile Arg Asp Ala Thr His Asn Phe Pro Glu Ala Arg
100 105 110

Lys Lys Tyr Ala Val Val Arg Phe Asn Tyr Ser Pro His Val Pro Pro
115 120 125

Asn Leu Ala Ile Leu Asn Leu Pro Thr Phe Ile Pro Glu Gln Phe Ala
130 135 140

Gln Leu Thr Ala Phe Leu His Asn Val Glu His Thr Glu Arg Ala Asn
145 150 155 160

Val Thr Gln Asn Ile Ser Glu Ala Gln Ile His Glu Trp Asn Leu Cys
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Ala Ser Arg Met Met Ser Phe Phe Val Arg Asn Pro Asn Trp
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<210> 31
<211> 178
<212> PRT
<213> Unknown

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Caenorabditis elegans

<400> 31

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Phe Met Met Arg Ile Ala Asp Ala Leu Lys Lys Ser Asn Asn Lys Val
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Val Cys Asp Arg Trp Phe Glu Asp Ser Lys Asn Ala Glu Glu Asn Met
        35                  40                  45

Leu His Trp Val Tyr Glu Gln Thr Lys Ile Ala Glu Lys Ile Ile Val
    50                  55                  60

Phe His Ser Ala Tyr Tyr His Pro Arg Cys Gly Ile Tyr Asp Val Ile
65                  70                  75                  80

Asn Asn Phe Phe Pro Cys Thr Asp Pro Arg Leu Ala His Ile Ala Leu
                85                  90                  95

Thr Pro Glu Ala Gln Arg Ser Val Pro Lys Glu Val Glu Tyr Val Leu
            100                 105                 110

Pro Arg Asp Gln Lys Leu Leu Glu Asp Ala Phe Asp Ile Thr Ile Ala
        115                 120                 125

Asp Pro Leu Val Ile Asp Ile Pro Ile Glu Asp Val Ala Ile Pro Glu
    130                 135                 140

Asn Val Pro Ile His His Glu Ser Cys Asp Ser Ile Asp Ser Arg Asn
145                 150                 155                 160

Asn Ser Lys Thr His Ser Thr Asp Ser Gly Val Ser Ser Leu Ser Ser
                165                 170                 175

Asn Ser
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(71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(72) Inventor: GORMAN, Daniel, M.; 6371 Central Avenue, Newark, CA 94560 (US).

(74) Agent: ZARADIC, Sandy; Schering-Plough Corporation, Patent Department, K-6-1, 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

Published:
— *with international search report*

(88) Date of publication of the international search report: 23 January 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/090358 A3

(54) Title: MAMMALIAN RECEPTOR PROTEINS; RELATED REAGENTS AND METHODS

(57) Abstract: Nucleic acids encoding mammalian, e.g., primate, receptors, purified receptor proteins and fragments thereof. Antibodies, both polyclonal and monoclonal, are also provided. Methods of using the compositions for both diagnostic and therapeutic utilities are described.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/16767

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C07K14/715 C07K16/18 G01N33/53 C12N5/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

SEQUENCE SEARCH, EMBL, EPO-Internal, MEDLINE, BIOSIS, WPI Data, PAJ, CHEM ABS Data, SCISEARCH, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 29408 A (IMMUNEX CORP) 26 September 1996 (1996-09-26) page 2, line 35 -page 15, line 4	1-18
X	YAO Z ET AL: "MOLECULAR CHARACTERIZATION OF THE HUMAN INTERLEUKIN (IL)-17 RECEPTOR" CYTOKINE, ACADEMIC PRESS LTD, PHILADELPHIA, PA, US, vol. 9, no. 11, November 1997 (1997-11), pages 794-800, XP000867704 ISSN: 1043-4666 page 795; figure 2	1-4,6, 12-15

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 August 2002	29.08.02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Steffen, P

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/16767

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL 'Online! EBI; 18 February 2000 (2000-02-18) BLOECKER ET AL.: "Homo sapiens mRNA; cDNA DKFZp434N1928" Database accession no. AL133097 XP002183453 the whole document ---	1-4,6, 12-15
A	WO 99 14240 A (HUMAN GENOME SCIENCES INC ;RUBEN STEVEN M (US); SHI YANGGU (US)) 25 March 1999 (1999-03-25) the whole document ---	
A	TIAN E ET AL: "EVI27 ENCODES A NOVEL MEMBRANE PROTEIN WITH HOMOLOGY TO THE IL17 RECEPOR" ONCOGENE, BASINGSTOKE, HANTS, GB, vol. 19, no. 17, 20 April 2000 (2000-04-20), pages 2098-2109, XP008000240 ISSN: 0950-9232 the whole document ---	
A	SHI YANGGU ET AL: "A novel cytokine receptor-ligand pair: Identification, molecular characterization, and in vivo immunomodulatory activity." JOURNAL OF BIOLOGICAL CHEMISTRY (JBC PAPERS IN PRESS, DOI 10.1074/JBC.M910228199), vol. 275, no. 25, 3 April 2000 (2000-04-03), pages 19167-19176, XP002197927 ISSN: 0021-9258 the whole document ---	
A	FOSSIEZ F ET AL: "INTERLEUKIN-17" INTERNATIONAL REVIEWS OF IMMUNOLOGY, HARWOOD ACADEMIC PUBLISHERS, LONDON, GB, vol. 16, no. 5/6, 1998, pages 541-551, XP000867763 ISSN: 0883-0185 the whole document ---	
E	WO 01 68859 A (AMGEN INC ;JING SHUQIAN (US)) 20 September 2001 (2001-09-20) page 2, line 19 -page 10, line 27; examples 1-4 ---	1-18
E	WO 01 46420 A (GENENTECH INC) 28 June 2001 (2001-06-28) page 5, line 1 -page 16, line 17; figures 17,18 --- -/--	1-18

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 55865 A (GENESIS RES & DEV CORP LTD) 4 November 1999 (1999-11-04) SEQ ID NO's 125 and 303 and corresponding cDNA's page 3 -page 17 ---	1-18
X	DATABASE EMBL 'Online! EBI; 22 July 1999 (1999-07-22) NCI-CGAP: "ty30c03.x1 NCI_CGAP_UT2 Homo sapiens cDNA clone IMAGE:2280580 3' mRNA sequence" Database accession no. AI861981 XP002209553 the whole document ---	12-18
X	DATABASE EMBL 'Online! EBI; 21 October 1999 (1999-10-21) MARRA ET AL.: "ul91g04.y1 Sugano mouse kidney mkia Mus musculus cDNA clone IMAGE:2159478 5', mRNA sequence" Database accession no. AW107583 XP002209554 the whole document -----	12-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/16767

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.: 19, 20
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-18 (all partly)

   Compositions comprising primate DCRS8 polypeptides and nucleic acid sequences (SEQ ID NO's 14 and 13, respectively) as well as further embodiments relating to the said polypeptides and nucleic acid sequences.

2. Claims: 1-18 (all partly)

   Compositions comprising primate or rodent DCRS9 polypeptides and nucleic acid sequences (SEQ ID NO's 16, 19 and 17, 20, respectively) as well as further embodiments relating to the said polypeptides and nucleic acid sequences.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 19, 20

Present claims 19 and 20 relate to a method defined by reference to a desirable characteristic or property, namely contacting a cell with an unspecified agonist or antagonist of a mammalian protein of the application (e.g. DCRS8 or DCRS9).

The claims cover all methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, no search has been carried out for claims 19 and 20.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/16767

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9629408 A	26-09-1996	AU 696775 B2	17-09-1998
		AU 5526396 A	08-10-1996
		CA 2215394 A1	26-09-1996
		EP 0817847 A1	14-01-1998
		JP 11503309 T	26-03-1999
		NO 974258 A	24-11-1997
		NZ 306653 A	29-03-1999
		US 6096305 A	01-08-2000
		US 6072033 A	06-06-2000
		US 6197525 B1	06-03-2001
		US 6191104 B1	20-02-2001
		US 6100235 A	08-08-2000
		US 6072037 A	06-06-2000
		WO 9629408 A1	26-09-1996
		US 5869286 A	09-02-1999
WO 9914240 A	25-03-1999	AU 9482498 A	05-04-1999
		EP 1015488 A1	05-07-2000
		WO 9914240 A1	25-03-1999
WO 0168859 A	20-09-2001	AU 4754501 A	24-09-2001
		WO 0168859 A2	20-09-2001
		US 2002045213 A1	18-04-2002
WO 0146420 A	28-06-2001	AU 2590901 A	03-07-2001
		WO 0146420 A2	28-06-2001
		AU 2055401 A	12-06-2001
		AU 2224800 A	28-09-2000
		AU 2596700 A	28-09-2000
		AU 2877900 A	28-09-2000
		AU 3514400 A	28-09-2000
		EP 1220905 A2	10-07-2002
		WO 0053754 A1	14-09-2000
		WO 0053756 A2	14-09-2000
		WO 0053758 A2	14-09-2000
		WO 0140466 A2	07-06-2001
		US 2002094416 A1	18-07-2002
		AU 3434601 A	12-06-2001
		AU 7573000 A	26-03-2001
		EP 1208202 A2	29-05-2002
		WO 0116318 A2	08-03-2001
		WO 0140465 A2	07-06-2001
		AU 2883600 A	28-09-2000
		AU 3381600 A	28-09-2000
		AU 3774300 A	18-12-2000
		AU 5152700 A	02-01-2001
		AU 5459900 A	18-12-2000
		AU 6391000 A	19-02-2001
		EP 1159419 A1	05-12-2001
		EP 1210418 A1	05-06-2002
		EP 1208195 A2	29-05-2002
		EP 1212417 A2	12-06-2002
		EP 1185648 A2	13-03-2002
		WO 0053757 A2	14-09-2000
		WO 0073454 A1	07-12-2000
		WO 0073445 A2	07-12-2000
		WO 0077037 A2	21-12-2000
		WO 0073348 A2	07-12-2000

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/16767

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0146420 A		WO 0073452 A2	07-12-2000
		WO 0109327 A2	08-02-2001
		US 2002072496 A1	13-06-2002
		US 2002072067 A1	13-06-2002
		US 2002072092 A1	13-06-2002
		US 2002072497 A1	13-06-2002
		AU 1916701 A	16-07-2001
		AU 6802801 A	24-09-2001
		WO 0149715 A2	12-07-2001
		WO 0168848 A2	20-09-2001
		US 2002098505 A1	25-07-2002
		US 2002098506 A1	25-07-2002
		US 2002098507 A1	25-07-2002
		US 2002090681 A1	11-07-2002
		US 2002010137 A1	24-01-2002
		US 2002058309 A1	16-05-2002
WO 9955865 A	04-11-1999	US 6150502 A	21-11-2000
		AU 3961499 A	16-11-1999
		CA 2327317 A1	04-11-1999
		CN 1307637 T	08-08-2001
		EP 1073740 A1	07-02-2001
		JP 2002512798 T	08-05-2002
		WO 9955865 A1	04-11-1999
		NZ 507728 A	28-06-2002

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60/220,664	25 July 2000 (25.07.2000)	US
PCT/US00/20710	28 July 2000 (28.07.2000)	US
60/222,695	2 August 2000 (02.08.2000)	US
09/643,657	17 August 2000 (17.08.2000)	US
PCT/US00/23522	23 August 2000 (23.08.2000)	US
PCT/US00/23328	24 August 2000 (24.08.2000)	US
60/230,978	7 September 2000 (07.09.2000)	US
60/000,000	15 September 2000 (15.09.2000)	US
09/664,610	18 September 2000 (18.09.2000)	US
09/665,350	18 September 2000 (18.09.2000)	US
60/242,922	24 October 2000 (24.10.2000)	US
09/709,238	8 November 2000 (08.11.2000)	US
PCT/US00/30952	8 November 2000 (08.11.2000)	US
PCT/US00/30873	10 November 2000 (10.11.2000)	US
PCT/US00/32678	1 December 2000 (01.12.2000)	US
09/747,259	20 December 2000 (20.12.2000)	US
PCT/US00/34956	20 December 2000 (20.12.2000)	US
09/767,609	22 January 2001 (22.01.2001)	US
09/796,498	28 February 2001 (28.02.2001)	US
PCT/US01/06520	28 February 2001 (28.02.2001)	US
PCT/US01/06666	1 March 2001 (01.03.2001)	US
09/802,706	9 March 2001 (09.03.2001)	US
09/808,689	14 March 2001 (14.03.2001)	US
09/816,744	22 March 2001 (22.03.2001)	US
09/828,366	5 April 2001 (05.04.2001)	US
09/854,208	10 May 2001 (10.05.2001)	US
09/854,280	10 May 2001 (10.05.2001)	US
09/866,028	25 May 2001 (25.05.2001)	US
09/866,034	25 May 2001 (25.05.2001)	US
PCT/US01/17092	25 May 2001 (25.05.2001)	US
09/870,574	30 May 2001 (30.05.2001)	US
PCT/US01/17443	30 May 2001 (30.05.2001)	US
PCT/US01/17800	1 June 2001 (01.06.2001)	US

(71) Applicant *(for all designated States except US)*: **GENENTECH, INC.** [US/US]; 1 DNA Way, South San Francisco, CA 94080-4990 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BAKER, Kevin, P.** [GB/US]; 14006 Indian Run Drive, Darnestown, MD 20878 (US). **FERRARA, Napoleone** [US/US]; #704, 2090 Pacific Avenue, San Francisco, CA 94109 (US). **GERBER, Hanspeter** [CH/US]; #5, 1121 Tennessee Street, San Francisco, CA 94107 (US). **GERRITSEN, Mary, E.** [CA/US]; 541 Parrott Drive, San Mateo, CA 94402 (US). **GODDARD, Audrey** [CA/US]; 110 Congo Street, San Francisco, CA 94131 (US). **GODOWSKI, Paul, J.** [US/US]; 2627 Easton Drive, Burlingame, CA 94010 (US). **GURNEY, Austin, L.** [US/US]; 1 Debbie Lane, Belmont, CA 94002 (US). **HILLAN, Kenneth, J.** [GB/US]; 64 Seward Street, San Francisco, CA 94114 (US). **MARSTERS, Scot, A.** [US/US]; 990 Cherry Street, San Carlos, CA 94070 (US). **PAN, James** [CA/US]; 2705 Coronet Boulevard, Belmont, CA 94002 (US). **PAONI, Nicholas, F.** [US/US]; 1756 Terrace Drive, Belmont, CA 94002 (US). **STEPHAN, Jean-Philippe, F.** [FR/US]; 320 C Lansdale Avenue, Millbrae, CA 94030 (US). **WATANABE, Colin, K.** [US/US]; 128 Corliss Drive, Moraga, CA 94556 (US). **WILLIAMS, P., Mickey** [US/US]; 509 Alto Avenue, Half Moon Bay, CA 94019 (US). **WOOD, William, I.** [US/US]; 35 Southdown Court, Hillsborough, CA 94010 (US). **YE, Weilan** [CN/US]; 119 Barkentine Street, Foster City, CA 94404 (US).

(74) Agents: **AGARWAL, Atulya, R.** et al.; c/o GENENTECH, INC., MS49, 1 DNA Way, South San Francisco, CA 94080-4990 (US).

[Continued on next page]

WO 02/00690 A2

(54) **Title:** COMPOSITIONS AND METHODS FOR THE DIAGNOSIS AND TREATMENT OF DISORDERS INVOLVING ANGIOGENESIS

(57) **Abstract:** Compositions and methods are disclosed for stimulating or inhibiting angiogenesis and/or cardiovascularization in mammals, including humans. Pharmaceutical compositions are based on polypeptides or antagonists thereto that have been identified for one or more of these uses. Disorders that can be diagnosed, prevented, or treated by the compositions herein include trauma such as wounds, various cancers, and disorders of the vessels including atherosclerosis and cardiac hypertrophy.In addition, the present invention is directed to novel polypeptides and to nucleic acid molecules encoding those polypeptides. Also provided herein are vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide molecules comprising the polypeptides of the present invention fused to heterologous polypeptide sequences, antibodies which bind to the polypeptides of the present invention and to methods for producing the polypeptides of the present invention.

(81) **Designated States** *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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COMPOSITIONS AND METHODS FOR THE DIAGNOSIS AND TREATMENT OF DISORDERS INVOLVING ANGIOGENESIS

1. Field of the Invention

The present invention relates to compositions and methods useful for the modulation (*e.g.*, promotion or inhibition) of angiogenesis and/or cardiovascularization in mammals in need of such biological effect. The present invention further relates to the diagnosis and treatment of disorders involving angiogenesis (*e.g.*, cardiovascular as well as oncological disorders).

2. Background of the Invention

2.1. Angiogenesis

Angiogenesis, defined as the growth or sprouting of new blood vessels from existing vessels, is a complex process that primarily occurs during embryonic development. Under normal physiological conditions in adults, angiogenesis takes place only in very restricted situations such as hair growth and wounding healing (Auerbach, W. and Auerbach, R., 1994, *Pharmacol Ther* 63(3):265-3 11; Ribatti et al.,1991, *Haematologica* 76(4):3 11-20; Risau, 1997, *Nature* 386(6626):67 1-4). Unregulated angiogenesis has gradually been recognized to be responsible for a wide range of disorders, including, but not limited to cardiovascular disease, cancer, rheumatoid arthritis, psoriasis and diabetic retinopathy (Folkman, 1995, *Nat Med* 1(1):27-31; Isner, 1999, *Circulation* 99(13): 1653-5; Koch, 1998, *Arthritis Rheum* 41(6):951-62; Walsh, 1999, *Rheumatology (Oxford)* 38(2):103-12; Ware and Simons, 1997, *Nat Med* 3(2): 158-64).

2.2. Cardiac Disorders and Factors

Heart failure affects approximately five million Americans, and new cases of heart failure number about 400,000 each year. It is the single most frequent cause of hospitalization for people age 65 and older in the United States. Recent advances in the management of acute cardiac diseases, including acute myocardial infarction, are resulting in an expanding patient population that will eventually develop chronic heart failure. From 1979 to 1995, hospitalizations for congestive heart failure (CHF) rose from 377,000 to 872,000 (a 130 percent increase) and CHF deaths increased 116 percent.

CHF is a syndrome characterized by left ventricular dysfunction, reduced exercise tolerance, impaired quality of life, and markedly shortened life expectancy. The sine qua non of heart failure is an inability of the heart to pump blood at a rate sufficient to meet the metabolic needs of the body's tissues (in other words, there is insufficient cardiac output).

At least four major compensatory mechanisms are activated in the setting of heart failure to boost cardiac output, including peripheral vasoconstriction, increased heart rate, increased cardiac contractility, and increased plasma volume. These effects are mediated primarily by the sympathetic nervous system and the renin-angiotensin system. *See*, Eichhorn, American Journal of Medicine, 104: 163-169 (1998). Increased output from the

sympathetic nervous system increases vascular tone, heart rate, and contractility. Angiotensin II elevates blood pressure by 1) directly stimulating vascular smooth muscle contraction, 2) promoting plasma volume expansion by stimulating aldosterone and antidiuretic hormone secretion, 3) stimulating sympathetic-mediated vascular tone, and 4) catalyzing the degradation of bradykinin, which has vasodilatory and natriuretic activity. *See*, review by Brown and Vaughan, Circulation, 97: 1411-1420 (1998). As noted below, angiotensin II may also have directly deleterious effects on the heart by promoting myocyte necrosis (impairing systolic function) and intracardiac fibrosis (impairing diastolic and in some cases systolic function). *See*, Weber, Circulation, 96: 4065-4082 (1998).

A consistent feature of congestive heart failure (CHF) is cardiac hypertrophy, an enlargement of the heart that is activated by both mechanical and hormonal stimuli and enables the heart to adapt to demands for increased cardiac output. Morgan and Baker, Circulation, 83: 13-25 (1991). This hypertrophic response is frequently associated with a variety of distinct pathological conditions such as hypertension, aortic stenosis, myocardial infarction, cardiomyopathy, valvular regurgitation, and intracardiac shunt, all of which result in chronic hemodynamic overload.

Hypertrophy is generally defined as an increase in size of an organ or structure independent of natural growth that does not involve tumor formation. Hypertrophy of the heart is due either to an increase in the mass of the individual cells (myocytes), or to an increase in the number of cells making up the tissue (hyperplasia), or both. While the enlargement of an embryonic heart is largely dependent on an increase in myocyte number (which continues until shortly after birth), post-natal cardiac myocytes lose their proliferative capacity. Further growth occurs through hypertrophy of the individual cells.

Adult myocyte hypertrophy is initially beneficial as a short term response to impaired cardiac function by permitting a decrease in the load on individual muscle fibers. With severe, long-standing overload, however, the hypertrophied cells begin to deteriorate and die. Katz, "Heart Failure", in: Katz A.M. ed., Physiology of the Heart (New York: Raven Press, 1992) pp. 638-668. Cardiac hypertrophy is a significant risk factor for both mortality and morbidity in the clinical course of heart failure. Katz, Trends Cardiovasc. Med., 5: 37-44 (1995). For further details of the causes and pathology of cardiac hypertrophy *see*, *e.g.*, Heart Disease, A Textbook of Cardiovascular Medicine, Braunwald, E. ed. (W.B. Saunders Co., 1988), Chapter 14, "Pathophysiology of Heart Failure."

On a cellular level, the heart is composed of myocytes and surrounding support cells, generically called non-myocytes. While non-myocytes are primarily fibroblast/mesenchymal cells, they also include endothelial and smooth muscle cells. Indeed, although myocytes make up most of the adult myocardial mass, they represent only about 30% of the total cell numbers present in heart. In response to hormonal, physiological, hemodynamic, and pathological stimuli, adult ventricular muscle cells can adapt to increased workloads through the activation of a hypertrophic process. This response is characterized by an increase in myocyte cell size and contractile protein content of individual cardiac muscle cells, without concomitant cell division and activation of embryonic genes, including the gene for atrial natriuretic peptide (ANP). Chien *et al.*, FASEB J., 5: 3037-3046 (1991); Chien *et al.*, Annu. Rev. Physiol., 55: 77-95 (1993). An increment in myocardial mass as a result of an increase in myocyte size that is associated with an accumulation of interstitial collagen within the extracellular matrix and around intramyocardial coronary arteries has been described in left ventricular hypertrophy secondary to pressure overload

in humans. Caspari *et al.*, Cardiovasc. Res., 11: 554-558 (1977); Schwarz *et al.*, Am. J. Cardiol., 42: 895-903 (1978); Hess *et al.*, Circulation, 63: 360-371 (1981); Pearlman *et al.*, Lab. Invest., 46: 158-164 (1982).

It has also been suggested that paracrine factors produced by non-myocyte supporting cells may additionally be involved in the development of cardiac hypertrophy, and various non-myocyte derived hypertrophic factors, such as, leukocyte inhibitory factor (LIF) and endothelin, have been identified. Metcalf, Growth Factors, 7: 169-173 (1992); Kurzrock *et al.*, Endocrine Reviews, 12: 208-217 (1991); Inoue *et al.*, Proc. Natl. Acad. Sci. USA, 86: 2863-2867 (1989); Yanagisawa and Masaki, Trends Pharm. Sci., 10: 374-378 (1989); U.S. Patent No. 5,573,762 (issued November 12, 1996). Further exemplary factors that have been identified as potential mediators of cardiac hypertrophy include cardiotrophin-1 (CT-1) (Pennica *et al.*, Proc. Nat. Acad. Sci. USA, 92: 1142-1146 (1995)), catecholamines, adrenocorticosteroids, angiotensin, and prostaglandins.

At present, the treatment of cardiac hypertrophy varies depending on the underlying cardiac disease. Catecholamines, adrenocorticosteroids, angiotensin, prostaglandins, LIF, endothelin (including endothelin-1, -2, and -3 and big endothelin), and CT-1 are among the factors identified as potential mediators of hypertrophy. For example, beta-adrenergic receptor blocking drugs (beta-blockers, *e.g.*, propranolol, timolol, tertalolol, carteolol, nadolol, betaxolol, penbutolol, acetobutolol, atenolol, metoprolol, carvedilol, etc.) and verapamil have been used extensively in the treatment of hypertrophic cardiomyopathy. The beneficial effects of beta-blockers on symptoms (*e.g.*, chest pain) and exercise tolerance are largely due to a decrease in the heart rate with a consequent prolongation of diastole and increased passive ventricular filling. Thompson *et al.*, Br. Heart J., 44: 488-98 (1980); Harrison *et al.*, Circulation, 29: 84-98 (1964). Verapamil has been described to improve ventricular filling and probably reducing myocardial ischemia. Bonow *et al.*, Circulation, 72: 853-64 (1985).

Nifedipine and diltiazem have also been used occasionally in the treatment of hypertrophic cardiomyopathy. Lorell *et al.*, Circulation, 65: 499-507 (1982); Betocchi *et al.*, Am. J. Cardiol., 78: 451-457 (1996). However, because of its potent vasodilating properties, nifedipine may be harmful, especially in patients with outflow obstruction. Disopyramide has been used to relieve symptoms by virtue of its negative inotropic properties. Pollick, N. Engl. J. Med., 307: 997-999 (1982). In many patients, however, the initial benefits decrease with time. Wigle *et al.*, Circulation, 92: 1680-1692 (1995). Antihypertensive drug therapy has been reported to have beneficial effects on cardiac hypertrophy associated with elevated blood pressure. Examples of drugs used in antihypertensive therapy, alone or in combination, are calcium antagonists, *e.g.*, nitrendipine; adrenergic receptor blocking agents, *e.g.*, those listed above; angiotensin converting enzyme (ACE) inhibitors such as quinapril, captopril, enalapril, ramipril, benazepril, fosinopril, and lisinopril; diuretics, *e.g.*, chlorothiazide, hydrochlorothiazide, hydroflumethazide, methylchlothiazide, benzthiazide, dichlorphenamide, acetazolamide, and indapamide; and calcium channel blockers, *e.g.*, diltiazem, nifedipine, verapamil, and nicardipine.

For example, treatment of hypertension with diltiazem and captopril showed a decrease in left ventricular muscle mass, but the Doppler indices of diastolic function did not normalize. Szlachcic *et al.*, Am. J. Cardiol., 63: 198-201 (1989); Shahi *et al.*, Lancet, 336: 458-461 (1990). These findings were interpreted to indicate that excessive amounts of interstitial collagen may remain after regression of left ventricular hypertrophy. Rossi *et al.*, Am. Heart J., 124: 700-709 (1992). Rossi *et al.*, *supra*, investigated the effect of captopril on the prevention and

regression of myocardial cell hypertrophy and interstitial fibrosis in pressure overload cardiac hypertrophy, in experimental rats.

Agents that increase cardiac contractility directly (iontropic agents) were initially thought to benefit patients with heart failure because they improved cardiac output in the short term. However, all positive inotropic agents except digoxigenin have been found to result in increased long-term mortality, in spite of short-term improvements in cardiac performance. Massie, Curr. Op. in Cardiology, 12: 209-217 (1997); Reddy *et al.*, Curr. Opin. Cardiol., 12: 233-241 (1997). Beta-adrenergic receptor blockers have recently been advocated for use in heart failure. Evidence from clinical trials suggests that improvements in cardiac function can be achieved without increased mortality, though documented improvements of patient survival have not yet been demonstrated. *See* also, U.S. Pat. Nos. 5,935,924, 5,624,806; 5,661,122; and 5,610,134 and WO 95/28173 regarding the use of cardiotropin-1 or antagonists thereof, or growth hormone and/or insulin-like growth factor-I in the treatment of CHF. Another treatment modality is heart transplantation, but this is limited by the availability of donor hearts.

Endothelin is a vasoconstricting peptide comprising 21 amino acids, isolated from swine arterial endothelial culture supernatant and structurally determined. Yanagisawa *et al.*, Nature, 332: 411-415 (1988). Endothelin was later found to exhibit various actions, and endothelin antibodies as endothelin antagonists have proven effective in the treatment of myocardial infarction, renal failure, and other diseases. Since endothelin is present in live bodies and exhibits vasoconstricting action, it is expected to be an endogenous factor involved in the regulation of the circulatory system, and may be associated with hypertension, cardiovascular diseases such as myocardial infarction, and renal diseases such as acute renal failure. Endothelin antagonists are described, for example, in U.S. Pat. No. 5,773,414; JP Pat. Publ. 3130299/1991, EP 457,195; EP 460,679; and EP 552,489. A new endothelin B receptor for identifying endothelin receptor antagonists is described in U.S. Pat. No. 5,773,223.

Current therapy for heart failure is primarily directed to using angiotensin-converting enzyme (ACE) inhibitors, such as captopril, and diuretics. These drugs improve hemodynamic profile and exercise tolerance and reduce the incidence of morbidity and mortality in patients with CHF. Kramer *et al.*, Circulation, 67(4): 807-816 (1983); Captopril Multicenter Research Group, J.A.C.C., 2(4): 755-763 (1983); The CONSENSUS Trial Study Group, N. Engl. J. Med., 316(23): 1429-1435 (1987); The SOLVD Investigators, N. Engl. J. Med., 325(5): 293-302 (1991). Further, they are useful in treating hypertension, left ventricular dysfunction, atherosclerotic vascular disease, and diabetic nephropathy. Brown and Vaughan, *supra*. However, despite proven efficacy, response to ACE inhibitors has been limited. For example, while prolonging survival in the setting of heart failure, ACE inhibitors appear to slow the progression towards end-stage heart failure, and substantial numbers of patients on ACE inhibitors have functional class III heart failure.

Moreover, improvement of functional capacity and exercise time is only small and mortality, although reduced, continues to be high. The CONSENSUS Trial Study Group, N. Engl. J. Med., 316(23): 1429-1453 (1987); The SOLVD Investigators, N. Engl. J. Med., 325(5): 293-302 (1991); Cohn *et al.*, N. Engl. J. Med., 325(5): 303-310 (1991); The Captopril-Digoxin Multicenter Research Group, JAMA, 259(4): 539-544 (1988). Hence, ACE inhibitors consistently appear unable to relieve symptoms in more than 60% of heart failure patients and reduce mortality of heart failure only by approximately 15-20%. For further adverse effects, *see* Brown and Vaughan,

supra.

An alternative to ACE inhibitors is represented by specific AT1 receptor antagonists. Clinical studies are planned to compare the efficacy of these two modalities in the treatment of cardiovascular and renal disease. However, animal model data suggests that the ACE/Ang II pathway, while clearly involved in cardiac hypertrophy, is not the only, or even the primary pathway active in this role. Mouse genetic "knockout" models have been made to test individual components of the pathway. In one such model, the primary cardiac receptor for Ang II, AT sub 1A, has been genetically deleted; these mice do not develop hypertrophy when Ang II is given experimentally (confirming the basic success of the model in eliminating hypertrophy secondary to Ang II). However, when the aorta is constricted in these animals (a model of hypertensive cardiac stress), the hearts still become hypertrophic. This suggests that alternative signaling pathways, not depending on this receptor (AT sub 1A), are activated in hypertension. ACE inhibitors would presumably not be able to inhibit these pathways. *See*, Harada *et al.*, Circulation, 97: 1952-1959 (1998). *See* also, Homcy, Circulation, 97: 1890-1892 (1998) regarding the enigma associated with the process and mechanism of cardiac hypertrophy.

About 750,000 patients suffer from acute myocardial infarction (AMI) annually, and approximately one-fourth of all deaths in the United States are due to AMI. In recent years, thrombolytic agents, *e.g.*, streptokinase, urokinase, and in particular tissue plasminogen activator (t-PA) have significantly increased the survival of patients who suffered myocardial infarction. When administered as a continuous intravenous infusion over 1.5 to 4 hours, t-PA produces coronary patency at 90 minutes in 69% to 90% of the treated patients. Topol *et al.*, Am. J. Cardiol., 61: 723-728 (1988); Neuhaus *et al.*, J. Am. Coll. Cardiol., 12: 581-587 (1988); Neuhaus *et al.*, J. Am. Coll. Cardiol., 14: 1566-1569 (1989). The highest patency rates have been reported with high dose or accelerated dosing regimens. Topol, J. Am. Coll. Cardiol., 15: 922-924 (1990). t-PA may also be administered as a single bolus, although due to its relatively short half-life, it is better suited for infusion therapy. Tebbe *et al.*, Am. J. Cardiol., 64: 448-453 (1989). A t-PA variant, specifically designed to have longer half-life and very high fibrin specificity, TNK t-PA (a T103N, N117Q, KHRR(296-299)AAAA t-PA variant, Keyt *et al.*, Proc. Natl. Acad. Sci. USA, 91: 3670-3674 (1994)) is particularly suitable for bolus administration. However, despite all these advances, the long-term prognosis of patient survival depends greatly on the post-infarction monitoring and treatment of the patients, which should include monitoring and treatment of cardiac hypertrophy.

2.3. Growth Factors

Various naturally occurring polypeptides reportedly induce the proliferation of endothelial cells. Among those polypeptides are the basic and acidic fibroblast growth factors (FGF) (Burgess and Maciag, Annual Rev. Biochem., 58: 575 (1989)), platelet-derived endothelial cell growth factor (PD-ECGF) (Ishikawa *et al.*, Nature, 338: 557 (1989)), and vascular endothelial growth factor (VEGF). Leung *et al.*, Science, 246: 1306 (1989); Ferrara and Henzel, Biochem. Biophys. Res. Commun., 161: 851 (1989); Tischer *et al.*, Biochem. Biophys. Res. Commun., 165: 1198 (1989); EP 471,754B granted July 31, 1996.

Media conditioned by cells transfected with the human VEGF (hVEGF) cDNA promoted the proliferation of capillary endothelial cells, whereas control cells did not. Leung *et al.*, Science, 246: 1306 (1989). Several

additional cDNAs were identified in human cDNA libraries that encode 121-, 189-, and 206-amino acid isoforms of hVEGF (also collectively referred to as hVEGF-related proteins). The 121-amino acid protein differs from hVEGF by virtue of the deletion of the 44 amino acids between residues 116 and 159 in hVEGF. The 189-amino acid protein differs from hVEGF by virtue of the insertion of 24 amino acids at residue 116 in hVEGF, and apparently is identical to human vascular permeability factor (hVPF). The 206-amino acid protein differs from hVEGF by virtue of an insertion of 41 amino acids at residue 116 in hVEGF. Houck *et al.*, Mol. Endocrin., 5: 1806 (1991); Ferrara *et al.*, J. Cell. Biochem., 47: 211 (1991); Ferrara *et al.*, Endocrine Reviews, 13: 18 (1992); Keck *et al.*, Science, 246: 1309 (1989); Connolly *et al.*, J. Biol. Chem., 264: 20017 (1989); EP 370,989 published May 30, 1990.

It is now well established that angiogenesis, which involves the formation of new blood vessels from preexisting endothelium, is implicated in the pathogenesis of a variety of disorders. These include solid tumors and metastasis, atherosclerosis, retrolental fibroplasia, hemangiomas, chronic inflammation, intraocular neovascular syndromes such as proliferative retinopathies, *e.g.*, diabetic retinopathy, age-related macular degeneration (AMD), neovascular glaucoma, immune rejection of transplanted corneal tissue and other tissues, rheumatoid arthritis, and psoriasis. Folkman *et al.*, J. Biol. Chem., 267: 10931-10934 (1992); Klagsbrun *et al.*, Annu. Rev. Physiol., 53: 217-239 (1991); and Garner A., "Vascular diseases", In: Pathobiology of Ocular Disease. A Dynamic Approach, Garner A., Klintworth GK, eds., 2nd Edition (Marcel Dekker, NY, 1994), pp 1625-1710.

In the case of tumor growth, angiogenesis appears to be crucial for the transition from hyperplasia to neoplasia, and for providing nourishment for the growth and metastasis of the tumor. Folkman *et al.*, Nature, 339: 58 (1989). The neovascularization allows the tumor cells to acquire a growth advantage and proliferative autonomy compared to the normal cells. A tumor usually begins as a single aberrant cell which can proliferate only to a size of a few cubic millimeters due to the distance from available capillary beds, and it can stay 'dormant' without further growth and dissemination for a long period of time. Some tumor cells then switch to the angiogenic phenotype to activate endothelial cells, which proliferate and mature into new capillary blood vessels. These newly formed blood vessels not only allow for continued growth of the primary tumor, but also for the dissemination and recolonization of metastatic tumor cells. Accordingly, a correlation has been observed between density of microvessels in tumor sections and patient survival in breast cancer as well as in several other tumors. Weidner *et al.*, N. Engl. J. Med, 324: 1-6 (1991); Horak *et al.*, Lancet, 340: 1120-1124 (1992); Macchiarini *et al.*, Lancet, 340: 145-146 (1992). The precise mechanisms that control the angiogenic switch is not well understood, but it is believed that neovascularization of tumor mass results from the net balance of a multitude of angiogenesis stimulators and inhibitors (Folkman, 1995, *Nat Med* 1(1):27-31).

The search for positive regulators of angiogenesis has yielded many candidates, including aFGF, bFGF, TGF-α, TGF-β, HGF, TNF-α, angiogenin, IL-8, etc. Folkman *et al.*, J.B.C., *supra*, and Klagsbrun *et al.*, *supra*. The negative regulators so far identified include thrombospondin (Good *et al.*, Proc. Natl. Acad. Sci. USA., 87: 6624-6628 (1990)), the 16-kilodalton N-terminal fragment of prolactin (Clapp *et al.*, Endocrinology, 133: 1292-1299 (1993)), angiostatin (O'Reilly *et al.*, Cell, 79: 315-328 (1994)), and endostatin. O'Reilly *et al.*, Cell, 88: 277-285 (1996).

Work done over the last several years has established the key role of VEGF, not only in stimulating vascular endothelial cell proliferation, but also in inducing vascular permeability and angiogenesis. Ferrara *et al.*, Endocr. Rev., 18: 4-25 (1997). The finding that the loss of even a single VEGF allele results in embryonic lethality points to an irreplaceable role played by this factor in the development and differentiation of the vascular system. Furthermore, VEGF has been shown to be a key mediator of neovascularization associated with tumors and intraocular disorders. Ferrara *et al.*, Endocr. Rev., *supra*. The VEGF mRNA is overexpressed by the majority of human tumors examined. Berkman *et al.*, J. Clin. Invest., 91: 153-159 (1993); Brown *et al.*, Human Pathol., 26: 86-91 (1995); Brown *et al.*, Cancer Res., 53: 4727-4735 (1993); Mattern *et al.*, Brit. J. Cancer, 73: 931-934 (1996); Dvorak *et al.*, Am. J. Pathol., 146: 1029-1039 (1995).

Also, the concentration levels of VEGF in eye fluids are highly correlated to the presence of active proliferation of blood vessels in patients with diabetic and other ischemia-related retinopathies. Aiello *et al.*, N. Engl. J. Med., 331: 1480-1487 (1994). Furthermore, recent studies have demonstrated the localization of VEGF in choroidal neovascular membranes in patients affected by AMD. Lopez *et al.*, Invest. Ophthalmol. Vis. Sci., 37: 855-868 (1996).

Anti-VEGF neutralizing antibodies suppress the growth of a variety of human tumor cell lines in nude mice (Kim *et al.*, Nature, 362: 841-844 (1993); Warren *et al.*, J. Clin. Invest., 95: 1789-1797 (1995); Borgström *et al.*, Cancer Res., 56: 4032-4039 (1996); Melnyk *et al.*, Cancer Res., 56: 921-924 (1996)) and also inhibit intraocular angiogenesis in models of ischemic retinal disorders. Adamis *et al.*, Arch. Ophthalmol., 114: 66-71 (1996). Therefore, anti-VEGF monoclonal antibodies or other inhibitors of VEGF action are promising candidates for the treatment of solid tumors and various intraocular neovascular disorders. Such antibodies are described, for example, in EP 817,648 published January 14, 1998 and in WO98/45331 and WO98/45332 both published October 15, 1998.

There exist several other growth factors and mitogens, including transforming oncogenes, that are capable of rapidly inducing a complex set of genes to be expressed by certain cells. Lau and Nathans, Molecular Aspects of Cellular Regulation, 6: 165-202 (1991). These genes, which have been named immediate-early- or early-response genes, are transcriptionally activated within minutes after contact with a growth factor or mitogen, independent of *de novo* protein synthesis. A group of these intermediate-early genes encodes secreted, extracellular proteins that are needed for coordination of complex biological processes such as differentiation and proliferation, regeneration, and wound healing. Ryseck *et al.*, Cell Growth Differ., 2: 235-233 (1991).

Highly-related proteins that belong to this group include *cef 10* (Simmons *et al.*, Proc. Natl. Acad. Sci. USA, 86: 1178-1182 (1989)), *cyr 61*, which is rapidly activated by serum- or platelet-derived growth factor (PDGF) (O'Brien *et al.*, Mol. Cell Biol., 10: 3569-3577 (1990), human connective tissue growth factor (CTGF) (Bradham *et al.*, J. Cell. Biol., 114: 1285-1294 (1991)), which is secreted by human vascular endothelial cells in high levels after activation with transforming growth factor beta (TGF-β), exhibits PDGF-like biological and immunological activities, and competes with PDGF for a particular cell surface receptor, *fisp-12* (Ryseck *et al.*, Cell Growth Differ., 2: 235-233 (1991)), human vascular IBP-like growth factor (VIGF) (WO 96/17931), and *nov*, normally arrested in adult kidney cells, which was found to be overexpressed in myeloblastosis-associated-virus-type-1-induced nephroblastomas. Joloit *et al.*, Mol. Cell. Biol., 12: 10-21 (1992).

The expression of these immediate-early genes acts as "third messengers" in the cascade of events triggered by growth factors. It is also thought that they are needed to integrate and coordinate complex biological processes, such as differentiation and wound healing in which cell proliferation is a common event.

As additional mitogens, insulin-like growth factor binding proteins (IGFBPs) have been shown, in complex with insulin-like growth factor (IGF), to stimulate increased binding of IGF to fibroblast and smooth muscle cell surface receptors. Clemmons *et al.*, J. Clin. Invest., 77: 1548 (1986). Inhibitory effects of IGFBP on various IGF actions *in vitro* include stimulation of glucose transport by adipocytes, sulfate incorporation by chondrocytes, and thymidine incorporation in fibroblast. Zapf *et al.*, J. Clin. Invest., 63: 1077 (1979). In addition, inhibitory effects of IGFBPs on growth factor-mediated mitogen activity in normal cells have been shown.

2.4. Need for Further Treatments

In view of the role of vascular endothelial cell growth and angiogenesis in many diseases and disorders, it is desirable to have a means of reducing or inhibiting one or more of the biological effects causing these processes. It is also desirable to have a means of assaying for the presence of pathogenic polypeptides in normal and diseased conditions, and especially cancer. Further, in a specific aspect, as there is no generally applicable therapy for the treatment of cardiac hypertrophy, the identification of factors that can prevent or reduce cardiac myocyte hypertrophy is of primary importance in the development of new therapeutic strategies to inhibit pathophysiological cardiac growth. While there are several treatment modalities for various cardiovascular and oncologic disorders, there is still a need for additional therapeutic approaches.

3. Summary of the Invention

The present invention provides compositions and methods for modulating (*e.g.*, promoting or inhibiting) angiogenesis and/or cardiovascularization in mammals. The present invention is based on the identification of compounds (*i.e.*, proteins) that test positive in various cardiovascular assays that test modulation (*e.g.*, promotion or inhibition) of certain biological activities. Accordingly, the compounds are believed to be useful drugs and/or drug components for the diagnosis and/or treatment (including prevention and amelioration) of disorders where such effects are desired, such as the promotion or inhibition of angiogenesis, inhibition or stimulation of vascular endothelial cell growth, stimulation of growth or proliferation of vascular endothelial cells, inhibition of tumor growth, inhibition of angiogenesis-dependent tissue growth, stimulation of angiogenesis-dependent tissue growth, inhibition of cardiac hypertrophy and stimulation of cardiac hypertrophy, *e.g.*, for the treatment of congestive heart failure. In addition, the compositions and methods of the invention provide for the diagnostic monitoring of patients undergoing clinical evaluation for the treatment of angiogenesis-related disorders, for monitoring the efficacy of compounds in clinical trials and for identifying subjects who may be predisposed to such angiogenic-related disorders.

In one embodiment, the present invention provides a composition comprising a PRO polypeptide, an agonist or antagonist thereof, or an anti-PRO antibody in admixture with a pharmaceutically acceptable carrier. In one aspect, the composition comprises a therapeutically effective amount of the polypeptide, agonist, antagonist

or antibody. In another aspect, the composition comprises a further active ingredient, namely, a cardiovascular, endothelial or angiogenic agent or an angiostatic agent, preferably an angiogenic or angiostatic agent. Preferably, the composition is sterile. The PRO polypeptide, agonist, antagonist or antibody may be administered in the form of a liquid pharmaceutical formulation, which may be preserved to achieve extended storage stability. Preserved liquid pharmaceutical formulations might contain multiple doses of PRO polypeptide, agonist, antagonist or antibody, and might, therefore, be suitable for repeated use. In a preferred embodiment, where the composition comprises an antibody, the antibody is a monoclonal antibody, an antibody fragment, a humanized antibody, or a single-chain antibody.

In a further embodiment, the present invention provides a method for preparing such a composition useful for the treatment of a cardiovascular, endothelial or angiogenic disorder comprising admixing a therapeutically effective amount of a PRO polypeptide, agonist, antagonist or antibody with a pharmaceutically acceptable carrier.

In a still further aspect, the present invention provides an article of manufacture comprising:

(a) a composition of matter comprising a PRO polypeptide or agonist or antagonist thereof;

(b) a container containing said composition; and

(c) a label affixed to said container, or a package insert included in said container referring to the use of said PRO polypeptide or agonist or antagonist thereof in the treatment of a cardiovascular, endothelial or angiogenic disorder, wherein the agonist or antagonist may be an antibody which binds to the PRO polypeptide. The composition may comprise a therapeutically effective amount of the PRO polypeptide or the agonist or antagonist thereof.

In another embodiment, the present invention provides a method for identifying an agonist of a PRO polypeptide comprising:

(a) contacting cells and a test compound to be screened under conditions suitable for the induction of a cellular response normally induced by a PRO polypeptide; and

(b) determining the induction of said cellular response to determine if the test compound is an effective agonist, wherein the induction of said cellular response is indicative of said test compound being an effective agonist.

In another embodiment, the present invention provides a method for identifying an agonist of a PRO polypeptide comprising:

(a) contacting cells and a test compound to be screened under conditions suitable for the stimulation of cell proliferation by a PRO polypeptide; and

(b) measuring the proliferation of said cells to determine if the test compound is an effective agonist, wherein the stimulation of cell proliferation is indicative of said test compound being an effective agonist.

In another embodiment, the invention provides a method for identifying a compound that inhibits the activity of a PRO polypeptide comprising contacting a test compound with a PRO polypeptide under conditions and for a time sufficient to allow the test compound and polypeptide to interact and determining whether the activity of the PRO polypeptide is inhibited. In a specific preferred aspect, either the test compound or the PRO polypeptide is immobilized on a solid support. In another preferred aspect, the non-immobilized component carries a detectable

label. In a preferred aspect, this method comprises the steps of:

(a) contacting cells and a test compound to be screened in the presence of a PRO polypeptide under conditions suitable for the induction of a cellular response normally induced by a PRO polypeptide; and

(b) determining the induction of said cellular response to determine if the test compound is an effective antagonist.

In another preferred aspect, this process comprises the steps of:

(a) contacting cells and a test compound to be screened in the presence of a PRO polypeptide under conditions suitable for the stimulation of cell proliferation by a PRO polypeptide; and

(b) measuring the proliferation of the cells to determine if the test compound is an effective antagonist.

In another embodiment, the invention provides a method for identifying a compound that inhibits the expression of a PRO polypeptide in cells that normally expresses the polypeptide, wherein the method comprises contacting the cells with a test compound and determining whether the expression of the PRO polypeptide is inhibited. In a preferred aspect, this method comprises the steps of:

(a) contacting cells and a test compound to be screened under conditions suitable for allowing expression of the PRO polypeptide; and

(b) determining the inhibition of expression of said polypeptide.

In a still further embodiment, the invention provides a compound that inhibits the expression of a PRO polypeptide, such as a compound that is identified by the methods set forth above.

Another aspect of the present invention is directed to an agonist or an antagonist of a PRO polypeptide which may optionally be identified by the methods described above.

One type of antagonist of a PRO polypeptide that inhibits one or more of the functions or activities of the PRO polypeptide is an antibody. Hence, in another aspect, the invention provides an isolated antibody that binds a PRO polypeptide. In a preferred aspect, the antibody is a monoclonal antibody, which preferably has non-human complementarity-determining-region (CDR) residues and human framework-region (FR) residues. The antibody may be labeled and may be immobilized on a solid support. In a further aspect, the antibody is an antibody fragment, a single-chain antibody, or a humanized antibody. Preferably, the antibody specifically binds to the polypeptide.

In a still further aspect, the present invention provides a method for diagnosing a disease or susceptibility to a disease which is related to a mutation in a PRO polypeptide-encoding nucleic acid sequence comprising determining the presence or absence of said mutation in the PRO polypeptide nucleic acid sequence, wherein the presence or absence of said mutation is indicative of the presence of said disease or susceptibility to said disease.

In a still further aspect, the invention provides a method of diagnosing a cardiovascular, endothelial or angiogenic disorder in a mammal which comprises analyzing the level of expression of a gene encoding a PRO polypeptide (a) in a test sample of tissue cells obtained from said mammal, and (b) in a control sample of known normal tissue cells of the same cell type, wherein a higher or lower expression level in the test sample as compared to the control sample is indicative of the presence of a cardiovascular, endothelial or angiogenic disorder in said mammal. The expression of a gene encoding a PRO polypeptide may optionally be accomplished by measuring

the level of mRNA or the polypeptide in the test sample as compared to the control sample.

In a still further aspect, the present invention provides a method of diagnosing a cardiovascular, endothelial or angiogenic disorder in a mammal which comprises detecting the presence or absence of a PRO polypeptide in a test sample of tissue cells obtained from said mammal, wherein the presence or absence of said PRO polypeptide in said test sample is indicative of the presence of a cardiovascular, endothelial or angiogenic disorder in said mammal.

In a still further embodiment, the invention provides a method of diagnosing a cardiovascular, endothelial or angiogenic disorder in a mammal comprising (a) contacting an anti-PRO antibody with a test sample of tissue cells obtained from the mammal, and (b) detecting the formation of a complex between the antibody and the PRO polypeptide in the test sample, wherein the formation of said complex is indicative of the presence of a cardiovascular, endothelial or angiogenic disorder in the mammal. The detection may be qualitative or quantitative, and may be performed in comparison with monitoring the complex formation in a control sample of known normal tissue cells of the same cell type. A larger or smaller quantity of complexes formed in the test sample indicates the presence of a cardiovascular, endothelial or angiogenic dysfunction in the mammal from which the test tissue cells were obtained. The antibody preferably carries a detectable label. Complex formation can be monitored, for example, by light microscopy, flow cytometry, fluorimetry, or other techniques known in the art. The test sample is usually obtained from an individual suspected to have a cardiovascular, endothelial or angiogenic disorder.

In another embodiment, the invention provides a method for determining the presence of a PRO polypeptide in a sample comprising exposing a sample suspected of containing the PRO polypeptide to an anti-PRO antibody and determining binding of said antibody to a component of said sample. In a specific aspect, the sample comprises a cell suspected of containing the PRO polypeptide and the antibody binds to the cell. The antibody is preferably detectably labeled and/or bound to a solid support.

In further aspects, the invention provides a cardiovascular, endothelial or angiogenic disorder diagnostic kit comprising an anti-PRO antibody and a carrier in suitable packaging. Preferably, such kit further comprises instructions for using said antibody to detect the presence of the PRO polypeptide. Preferably, the carrier is a buffer, for example. Preferably, the cardiovascular, endothelial or angiogenic disorder is cancer.

In yet another embodiment, the present invention provides a method for treating a cardiovascular, endothelial or angiogenic disorder in a mammal comprising administering to the mammal an effective amount of a PRO polypeptide. Preferably, the disorder is cardiac hypertrophy, trauma such as wounds or burns, or a type of cancer. In a further aspect, the mammal is further exposed to angioplasty or a drug that treats cardiovascular, endothelial or angiogenic disorders such as ACE inhibitors or chemotherapeutic agents if the cardiovascular, endothelial or angiogenic disorder is a type of cancer. Preferably, the mammal is human, preferably one who is at risk of developing cardiac hypertrophy and more preferably has suffered myocardial infarction.

In another preferred aspect, the cardiac hypertrophy is characterized by the presence of an elevated level of $PGF_{2\alpha}$. Alternatively, the cardiac hypertrophy may be induced by myocardial infarction, wherein preferably the administration of the PRO polypeptide is initiated within 48 hours, more preferably within 24 hours, following myocardial infarction.

In another preferred embodiment, the cardiovascular, endothelial or angiogenic disorder is cardiac hypertrophy and said PRO polypeptide is administered together with a cardiovascular, endothelial or angiogenic agent. The preferred cardiovascular, endothelial or angiogenic agent for this purpose is selected from the group consisting of an antihypertensive drug, an ACE inhibitor, an endothelin receptor antagonist and a thrombolytic agent. If a thrombolytic agent is administered, preferably the PRO polypeptide is administered following administration of such agent. More preferably, the thrombolytic agent is recombinant human tissue plasminogen activator.

In another preferred aspect, the cardiovascular, endothelial or angiogenic disorder is cardiac hypertrophy and the PRO polypeptide is administered following primary angioplasty for the treatment of acute myocardial infarction, preferably wherein the mammal is further exposed to angioplasty or a cardiovascular, endothelial, or angiogenic agent.

In another preferred embodiment, the cardiovascular, endothelial or angiogenic disorder is a cancer and the PRO polypeptide is administered in combination with a chemotherapeutic agent, a growth inhibitory agent or a cytotoxic agent.

In a further embodiment, the invention provides a method for treating a cardiovascular, endothelial or angiogenic disorder in a mammal comprising administering to the mammal an effective amount of a PRO polypeptide agonist, antagonist or anti-PRO antibody. Preferably, the cardiovascular, endothelial or angiogenic disorder is cardiac hypertrophy, trauma, a cancer, or age-related macular degeneration. Also preferred is where the mammal is human, and where an effective amount of an angiogenic or angiostatic agent is administered in conjunction with the agonist, antagonist or anti-PRO antibody.

In still further embodiments, the invention provides a method for treating a cardiovascular, endothelial or angiogenic disorder in a mammal that suffers therefrom comprising administering to the mammal a nucleic acid molecule that codes for either (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide or (c) an antagonist of a PRO polypeptide, wherein said agonist or antagonist may be an anti-PRO antibody. In a preferred embodiment, the mammal is human. In another preferred embodiment, the gene is administered via *ex vivo* gene therapy. In a further preferred embodiment, the gene is comprised within a vector, more preferably an adenoviral, adeno-associated viral, lentiviral, or retroviral vector.

In yet another aspect, the invention provides a recombinant retroviral particle comprising a retroviral vector consisting essentially of a promoter, nucleic acid encoding (a) a PRO polypeptide, (b) an agonist polypeptide of a PRO polypeptide, or (c) an antagonist polypeptide of a PRO polypeptide, and a signal sequence for cellular secretion of the polypeptide, wherein the retroviral vector is in association with retroviral structural proteins. Preferably, the signal sequence is from a mammal, such as from a native PRO polypeptide.

In a still further embodiment, the invention supplies an *ex vivo* producer cell comprising a nucleic acid construct that expresses retroviral structural proteins and also comprises a retroviral vector consisting essentially of a promoter, nucleic acid encoding (a) a PRO polypeptide, (b) an agonist polypeptide of a PRO polypeptide or (c) an antagonist polypeptide of a PRO polypeptide, and a signal sequence for cellular secretion of the polypeptide, wherein said producer cell packages the retroviral vector in association with the structural proteins to produce

recombinant retroviral particles.

In yet another embodiment, the invention provides a method for inhibiting endothelial cell growth in a mammal comprising administering to the mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein endothelial cell growth in said mammal is inhibited, and wherein said agonist or antagonist may be an anti-PRO antibody. Preferably, the mammal is human and the endothelial cell growth is associated with a tumor or a retinal disorder.

In yet another embodiment, the invention provides a method for stimulating endothelial cell growth in a mammal comprising administering to the mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein endothelial cell growth in said mammal is stimulated, and wherein said agonist or antagonist may be an anti-PRO antibody. Preferably, the mammal is human.

In yet another embodiment, the invention provides a method for inhibiting cardiac hypertrophy in a mammal comprising administering to the mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein cardiac hypertrophy in said mammal is inhibited, and wherein said agonist or antagonist may be an anti-PRO antibody. Preferably, the mammal is human and the cardiac hypertrophy has been induced by myocardial infarction.

In yet another embodiment, the invention provides a method for stimulating cardiac hypertrophy in a mammal comprising administering to the mammal (a) a PRO polypeptide, (b) an agonist of a PRO polypeptide, or (c) an antagonist of a PRO polypeptide, wherein cardiac hypertrophy in said mammal is stimulated, and wherein said agonist or antagonist may be an anti-PRO antibody. Preferably, the mammal is human who suffers from congestive heart failure.

In yet another embodiment, the invention provides a method for inhibiting angiogenesis induced by a PRO polypeptide in a mammal comprising administering a therapeutically effective amount of an anti-PRO antibody to the mammal. Preferably, the mammal is a human, and more preferably the mammal has a tumor or a retinal disorder.

In yet another embodiment, the invention provides a method for stimulating angiogenesis induced by a PRO polypeptide in a mammal comprising administering a therapeutically effective amount of a PRO polypeptide to the mammal. Preferably, the mammal is a human, and more preferably angiogenesis would promote tissue regeneration or wound healing.

In yet another embodiment, the invention provides a method for modulating (*e.g.*, inhibiting or stimulating) endothelial cell growth in a mammal comprising administering to the mammal a PRO21, PRO181, PRO205, PRO214, PRO221, PRO229, PRO231, PRO238, PRO241, PRO247, PRO256, PRO258, PRO263, PRO265, PRO295, PRO321, PRO322, PRO337, PRO363, PRO365, PRO444, PRO533, PRO697, PRO720, PRO725, PRO771, PRO788, PRO791, PRO819, PRO827, PRO828, PRO836, PRO846, PRO865, PRO1005, PRO1006, PRO1007, PRO1025, PRO1029, PRO1054, PRO1071, PRO1075, PRO1079, PRO1080, PRO1114, PRO1131, PRO1155, PRO1160, PRO1184, PRO1186, PRO1190, PRO1192, PRO1195, PRO1244, PRO1272, PRO1273, PRO1274, PRO1279, PRO1283, PRO1286, PRO1306, PRO1309, PRO1325, PRO1329, PRO1347, PRO1356, PRO1376, PRO1382, PRO1411, PRO1412, PRO1419, PRO1474, PRO1477, PRO1488, PRO1508, PRO1550,

PRO1556, PRO1760, PRO1782, PRO1787, PRO1801, PRO1868, PRO1887, PRO1890, PRO3438, PRO3444, PRO4302, PRO4324, PRO4333, PRO4341, PRO4342, PRO4353, PRO4354, PRO4356, PRO4371, PRO4405, PRO4408, PRO4422, PRO4425, PRO4499, PRO5723, PRO5725, PRO5737, PRO5776, PRO6006, PRO6029, PRO6071, PRO7436, PRO9771, PRO9821, PRO9873, PRO10008, PRO10096, PRO19670, PRO20040, PRO20044, PRO21055, PRO21384 or PRO28631 polypeptide, agonist or antagonist thereof, wherein endothelial cell growth in said mammal is modulated.

In yet another embodiment, the invention provides a method for modulating (*e.g.*, inhibiting or stimulating) smooth muscle cell growth in a mammal comprising administering to the mammal a PRO162, PRO181, PRO182, PRO195, PRO204, PRO221, PRO230, PRO256, PRO258, PRO533, PRO697, PRO725, PRO738, PRO826, PRO836, PRO840, PRO846, PRO865, PRO982, PRO1025, PRO1029, PRO1071, PRO1080, PRO1083, PRO1134, PRO1160, PRO1182, PRO1184, PRO1186, PRO1192, PRO1265, PRO1274, PRO1279, PRO1283, PRO1306, PRO1308, PRO1309, PRO1325, PRO1337, PRO1338, PRO1343, PRO1376, PRO1387, PRO1411, PRO1412, PRO1415, PRO1434, PRO1474, PRO1488, PRO1550, PRO1556, PRO1567, PRO1600, PRO1754, PRO1758, PRO1760, PRO1787, PRO1865, PRO1868, PRO1917, PRO1928, PRO3438, PRO3562, PRO4302, PRO4333, PRO4345, PRO4353, PRO4354, PRO4405, PRO4408, PRO4430, PRO4503, PRO5725, PRO6714, PRO9771, PRO9820, PRO9940, PRO10096, PRO21055, PRO21184 or PRO21366 polypeptide, agonist or antagonist thereof, wherein endothelial cell growth in said mammal is modulated.

In yet another embodiment, the invention provides a method for modulating (*e.g.*, inducing or reducing) cardiac hypertrophy in a mammal comprising administering to the mammal a PRO21 polypeptide, agonist or antagonist thereof, wherein cardiac hypertrophy in said mammal is modulated.

In yet another embodiment, the invention provides a method for modulating (*e.g.*, inducing or reducing) endothelial cell apoptosis in a mammal comprising administering to the mammal a PRO4302 polypeptide, agonist or antagonist thereof, wherein cardiac hypertrophy in said mammal is modulated.

In yet another embodiment, the invention provides a method for modulating (*e.g.*, stimulating or inhibiting) angiogenesis in a mammal comprising administering a therapeutically effective amount of a PRO1376 or PRO1449 polypeptide, agonist or antagonist thereof to the mammal, wherein said angiogenesis is modulated.

In yet another embodiment, the invention provides a method for modulating (*e.g.*, inducing or reducing) angiogenesis by modulating (*e.g.*, inducing or reducing) endothelial cell tube formation in a mammal comprising administering to the mammal a PRO178, PRO195, PRO228, PRO301, PRO302, PRO532, PRO724, PRO730, PRO734, PRO793, PRO871, PRO938, PRO1012, PRO1120, PRO1139, PRO1198, PRO1287, PRO1361, PRO1864, PRO1873, PRO2010, PRO3579, PRO4313, PRO4527, PRO4538, PRO4553, PRO4995, PRO5730, PRO6008, PRO7223, PRO7248 or PRO7261 polypeptide, agonist or antagonist thereof, wherein endothelial cell tube formation in said mammal is modulated.

In other embodiments of the present invention, the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a PRO polypeptide.

In one aspect, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98%

nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule encoding a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule comprising the coding sequence of a full-length PRO polypeptide cDNA as disclosed herein, the coding sequence of a PRO polypeptide lacking the signal peptide as disclosed herein, the coding sequence of an extracellular domain of a transmembrane PRO polypeptide, with or without the signal peptide, as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In a further aspect, the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule that encodes the same mature polypeptide encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein, or (b) the complement of the DNA molecule of (a).

Another aspect of the present invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide are disclosed herein. Therefore, soluble extracellular domains of the herein described PRO polypeptides are contemplated.

Another embodiment is directed to fragments of a PRO polypeptide coding sequence, or the complement thereof, that may find use as, for example, hybridization probes, for encoding fragments of a PRO polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-PRO antibody or as antisense oligonucleotide probes. Such nucleic acid fragments are usually at least about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 250, 300, 350, 400, 450, 500, 600, 700 or 800 nucleotides in length and alternatively at least about 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel fragments of a PRO polypeptide-encoding nucleotide sequence may be determined in a routine manner by aligning the PRO polypeptide-encoding nucleotide sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which PRO polypeptide-encoding nucleotide sequence fragment(s) are novel. All of such PRO polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the PRO polypeptide fragments encoded by these nucleotide molecule fragments, preferably those PRO polypeptide fragments that comprise a binding site for an anti-PRO antibody.

In another embodiment, the invention provides an isolated PRO polypeptide encoded by any of the isolated

nucleic acid sequences hereinabove identified.

In a certain aspect, the invention provides an isolated PRO polypeptide comprising an amino acid sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a PRO polypeptide having a full-length amino aoid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein.

In a further aspect, the invention provides an isolated PRO polypeptide comprising an amino acid sequence having at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to an amino acid sequence encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein.

In a specific aspect, the invention provides an isolated PRO polypeptide without the N-terminal signal sequence and/or the initiating methionine and that is encoded by a nucleotide sequence that encodes such an amino acid sequence as hereinbefore described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

Another aspect of the invention provides an isolated PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

In yet another embodiment, the invention provides agonists and antagonists of a native PRO polypeptide as defined herein. In a particular embodiment, the agonist or antagonist is an anti-PRO antibody or a small molecule.

In a further embodiment, the invention provides a method of identifying agonists or antagonists to a PRO polypeptide which comprise contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide. Preferably, the PRO polypeptide is a native PRO polypeptide.

In a still further embodiment, the invention provides a composition of matter comprising a PRO polypeptide, or an agonist or antagonist of a PRO polypeptide as herein described, or an anti-PRO antibody, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

Another embodiment of the present invention is directed to the use of a PRO polypeptide, or an agonist or antagonist thereof as hereinbefore described, or an anti-PRO antibody, for the preparation of a medicament useful in the treatment of a condition which is responsive to the PRO polypeptide, an agonist or antagonist thereof or an anti-PRO antibody.

In additional embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described polypeptides. Host cells comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli*, yeast, or Baculovirus-infected insect cells. A process for producing any of the herein described polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

In other embodiments, the invention provides chimeric molecules comprising any of the herein described polypeptides fused to a heterologous polypeptide or amino acid sequence. Example of such chimeric molecules comprise any of the herein described polypeptides fused to an epitope tag sequence or a Fc region of an immunoglobulin.

In yet another embodiment, the invention provides an antibody which specifically binds to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, humanized antibody, antibody fragment or single-chain antibody.

In yet other embodiments, the invention provides oligonucleotide probes useful for isolating genomic and cDNA nucleotide sequences or as antisense probes, wherein those probes may be derived from any of the above or below described nucleotide sequences.

4. Brief Description of the Drawings

Figure 1 shows a nucleotide sequence (SEQ ID NO:1) of a native sequence PRO181 cDNA, wherein SEQ ID NO:1 is a clone designated herein as "DNA23330-1390".

Figure 2 shows the amino acid sequence (SEQ ID NO:2) derived from the coding sequence of SEQ ID NO:1 shown in Figure 1.

Figure 3 shows a nucleotide sequence (SEQ ID NO:3) of a native sequence PRO178 cDNA, wherein SEQ ID NO:3 is a clone designated herein as "DNA23339-1130".

Figure 4 shows the amino acid sequence (SEQ ID NO:4) derived from the coding sequence of SEQ ID NO:3 shown in Figure 3.

Figure 5 shows a nucleotide sequence (SEQ ID NO:5) of a native sequence PRO444 cDNA, wherein SEQ ID NO:5 is a clone designated herein as "DNA26846-1397".

Figure 6 shows the amino acid sequence (SEQ ID NO:6) derived from the coding sequence of SEQ ID NO:5 shown in Figure 5.

Figure 7 shows a nucleotide sequence (SEQ ID NO:7) of a native sequence PRO195 cDNA, wherein SEQ ID NO:7 is a clone designated herein as "DNA26847-1395".

Figure 8 shows the amino acid sequence (SEQ ID NO:8) derived from the coding sequence of SEQ ID NO:7 shown in Figure 7.

Figure 9 shows a nucleotide sequence (SEQ ID NO:9) of a native sequence PRO182 cDNA, wherein SEQ ID NO:9 is a clone designated herein as "DNA27865-1091".

Figure 10 shows the amino acid sequence (SEQ ID NO:10) derived from the coding sequence of SEQ ID

NO:9 shown in Figure 9.

Figure 11 shows a nucleotide sequence (SEQ ID NO:11) of a native sequence PRO205 cDNA, wherein SEQ ID NO:11 is a clone designated herein as "DNA30868-1156".

Figure 12 shows the amino acid sequence (SEQ ID NO:12) derived from the coding sequence of SEQ ID NO:11 shown in Figure 11.

Figure 13 shows a nucleotide sequence (SEQ ID NO:13) of a native sequence PRO204 cDNA, wherein SEQ ID NO:13 is a clone designated herein as "DNA30871-1157".

Figure 14 shows the amino acid sequence (SEQ ID NO:14) derived from the coding sequence of SEQ ID NO:13 shown in Figure 13.

Figure 15 shows a nucleotide sequence (SEQ ID NO:15) of a native sequence PRO1873 cDNA, wherein SEQ ID NO:15 is a clone designated herein as "DNA30880".

Figure 16 shows the amino acid sequence (SEQ ID NO:16) derived from the coding sequence of SEQ ID NO:15 shown in Figure 15.

Figure 17 shows a nucleotide sequence (SEQ ID NO:17) of a native sequence PRO214 cDNA, wherein SEQ ID NO:17 is a clone designated herein as "DNA32286-1191".

Figure 18 shows the amino acid sequence (SEQ ID NO:18) derived from the coding sequence of SEQ ID NO:17 shown in Figure 17.

Figure 19 shows a nucleotide sequence (SEQ ID NO:19) of a native sequence PRO221 cDNA, wherein SEQ ID NO:19 is a clone designated herein as "DNA33089-1132".

Figure 20 shows the amino acid sequence (SEQ ID NO:20) derived from the coding sequence of SEQ ID NO:19 shown in Figure 19.

Figure 21 shows a nucleotide sequence (SEQ ID NO:21) of a native sequence PRO228 cDNA, wherein SEQ ID NO:21 is a clone designated herein as "DNA33092-1202".

Figure 22 shows the amino acid sequence (SEQ ID NO:22) derived from the coding sequence of SEQ ID NO:21 shown in Figure 21.

Figure 23 shows a nucleotide sequence (SEQ ID NO:23) of a native sequence PRO229 cDNA, wherein SEQ ID NO:23 is a clone designated herein as "DNA33100-1159".

Figure 24 shows the amino acid sequence (SEQ ID NO:24) derived from the coding sequence of SEQ ID NO:23 shown in Figure 23.

Figure 25 shows a nucleotide sequence (SEQ ID NO:25) of a native sequence PRO230 cDNA, wherein SEQ ID NO:25 is a clone designated herein as "DNA33223-1136".

Figure 26 shows the amino acid sequence (SEQ ID NO:26) derived from the coding sequence of SEQ ID NO:25 shown in Figure 25.

Figure 27 shows a nucleotide sequence (SEQ ID NO:27) of a native sequence PRO7223 cDNA, wherein SEQ ID NO:27 is a clone designated herein as "DNA34385".

Figure 28 shows the amino acid sequence (SEQ ID NO:28) derived from the coding sequence of SEQ ID NO:27 shown in Figure 27.

Figure 29 shows a nucleotide sequence (SEQ ID NO:29) of a native sequence PRO241 cDNA, wherein SEQ ID NO:29 is a clone designated herein as "DNA34392-1170".

Figure 30 shows the amino acid sequence (SEQ ID NO:30) derived from the coding sequence of SEQ ID NO:29 shown in Figure 29.

Figure 31 shows a nucleotide sequence (SEQ ID NO:31) of a native sequence PRO263 cDNA, wherein SEQ ID NO:31 is a clone designated herein as "DNA34431-1177".

Figure 32 shows the amino acid sequence (SEQ ID NO:32) derived from the coding sequence of SEQ ID NO:31 shown in Figure 31.

Figure 33 shows a nucleotide sequence (SEQ ID NO:33) of a native sequence PRO321 cDNA, wherein SEQ ID NO:33 is a clone designated herein as "DNA34433-1308".

Figure 34 shows the amino acid sequence (SEQ ID NO:34) derived from the coding sequence of SEQ ID NO:33 shown in Figure 33.

Figure 35 shows a nucleotide sequence (SEQ ID NO:35) of a native sequence PRO231 cDNA, wherein SEQ ID NO:35 is a clone designated herein as "DNA34434-1139".

Figure 36 shows the amino acid sequence (SEQ ID NO:36) derived from the coding sequence of SEQ ID NO:35 shown in Figure 35.

Figure 37 shows a nucleotide sequence (SEQ ID NO:37) of a native sequence PRO238 cDNA, wherein SEQ ID NO:37 is a clone designated herein as "DNA35600-1162".

Figure 38 shows the amino acid sequence (SEQ ID NO:38) derived from the coding sequence of SEQ ID NO:37 shown in Figure 37.

Figure 39 shows a nucleotide sequence (SEQ ID NO:39) of a native sequence PRO247 cDNA, wherein SEQ ID NO:39 is a clone designated herein as "DNA35673-1201".

Figure 40 shows the amino acid sequence (SEQ ID NO:40) derived from the coding sequence of SEQ ID NO:39 shown in Figure 39.

Figure 41 shows a nucleotide sequence (SEQ ID NO:41) of a native sequence PRO256 cDNA, wherein SEQ ID NO:41 is a clone designated herein as "DNA35880-1160".

Figure 42 shows the amino acid sequence (SEQ ID NO:42) derived from the coding sequence of SEQ ID NO:41 shown in Figure 41.

Figure 43 shows a nucleotide sequence (SEQ ID NO:43) of a native sequence PRO258 cDNA, wherein SEQ ID NO:43 is a clone designated herein as "DNA35918-1174".

Figure 44 shows the amino acid sequence (SEQ ID NO:44) derived from the coding sequence of SEQ ID NO:43 shown in Figure 43.

Figure 45 shows a nucleotide sequence (SEQ ID NO:45) of a native sequence PRO265 cDNA, wherein SEQ ID NO:45 is a clone designated herein as "DNA36350-1158".

Figure 46 shows the amino acid sequence (SEQ ID NO:46) derived from the coding sequence of SEQ ID NO:45 shown in Figure 45.

Figure 47 shows a nucleotide sequence (SEQ ID NO:47) of a native sequence PRO21 cDNA, wherein SEQ

ID NO:47 is a clone designated herein as "DNA36638-1056".

Figure 48 shows the amino acid sequence (SEQ ID NO:48) derived from the coding sequence of SEQ ID NO:47 shown in Figure 47.

Figure 49 shows a nucleotide sequence (SEQ ID NO:49) of a native sequence PRO295 cDNA, wherein SEQ ID NO:49 is a clone designated herein as "DNA38268-1188".

Figure 50 shows the amino acid sequence (SEQ ID NO:50) derived from the coding sequence of SEQ ID NO:49 shown in Figure 49.

Figure 51 shows a nucleotide sequence (SEQ ID NO:51) of a native sequence PRO302 cDNA, wherein SEQ ID NO:51 is a clone designated herein as "DNA40370-1217".

Figure 52 shows the amino acid sequence (SEQ ID NO:52) derived from the coding sequence of SEQ ID NO:51 shown in Figure 51.

Figure 53 shows a nucleotide sequence (SEQ ID NO:53) of a native sequence PRO301 cDNA, wherein SEQ ID NO:53 is a clone designated herein as "DNA40628-1216".

Figure 54 shows the amino acid sequence (SEQ ID NO:54) derived from the coding sequence of SEQ ID NO:53 shown in Figure 53.

Figure 55 shows a nucleotide sequence (SEQ ID NO:55) of a native sequence PRO337 cDNA, wherein SEQ ID NO:55 is a clone designated herein as "DNA43316-1237".

Figure 56 shows the amino acid sequence (SEQ ID NO:56) derived from the coding sequence of SEQ ID NO:55 shown in Figure 55.

Figure 57 shows a nucleotide sequence (SEQ ID NO:57) of a native sequence PRO7248 cDNA, wherein SEQ ID NO:57 is a clone designated herein as "DNA44195".

Figure 58 shows the amino acid sequence (SEQ ID NO:58) derived from the coding sequence of SEQ ID NO:57 shown in Figure 57.

Figure 59 shows a nucleotide sequence (SEQ ID NO:59) of a native sequence PRO846 cDNA, wherein SEQ ID NO:59 is a clone designated herein as "DNA44196-1353".

Figure 60 shows the amino acid sequence (SEQ ID NO:60) derived from the coding sequence of SEQ ID NO:59 shown in Figure 59.

Figure 61 shows a nucleotide sequence (SEQ ID NO:61) of a native sequence PRO1864 cDNA, wherein SEQ ID NO:61 is a clone designated herein as "DNA45409-2511".

Figure 62 shows the amino acid sequence (SEQ ID NO:62) derived from the coding sequence of SEQ ID NO:61 shown in Figure 61.

Figure 63 shows a nucleotide sequence (SEQ ID NO:63) of a native sequence PRO363 cDNA, wherein SEQ ID NO:63 is a clone designated herein as "DNA45419-1252".

Figure 64 shows the amino acid sequence (SEQ ID NO:64) derived from the coding sequence of SEQ ID NO:63 shown in Figure 63.

Figure 65 shows a nucleotide sequence (SEQ ID NO:65) of a native sequence PRO730 cDNA, wherein SEQ ID NO:65 is a clone designated herein as "DNA45624-1400".

Figure 66 shows the amino acid sequence (SEQ ID NO:66) derived from the coding sequence of SEQ ID NO:65 shown in Figure 65.

Figure 67 shows a nucleotide sequence (SEQ ID NO:67) of a native sequence PRO365 cDNA, wherein SEQ ID NO:67 is a clone designated herein as "DNA46777-1253".

Figure 68 shows the amino acid sequence (SEQ ID NO:68) derived from the coding sequence of SEQ ID NO:67 shown in Figure 67.

Figure 69 shows a nucleotide sequence (SEQ ID NO:69) of a native sequence PRO532 cDNA, wherein SEQ ID NO:69 is a clone designated herein as "DNA48335".

Figure 70 shows the amino acid sequence (SEQ ID NO:70) derived from the coding sequence of SEQ ID NO:69 shown in Figure 69.

Figure 71 shows a nucleotide sequence (SEQ ID NO:71) of a native sequence PRO322 cDNA, wherein SEQ ID NO:71 is a clone designated herein as "DNA48336-1309".

Figure 72 shows the amino acid sequence (SEQ ID NO:72) derived from the coding sequence of SEQ ID NO:71 shown in Figure 71.

Figure 73 shows a nucleotide sequence (SEQ ID NO:73) of a native sequence PRO1120 cDNA, wherein SEQ ID NO:73 is a clone designated herein as "DNA48606-1479".

Figure 74 shows the amino acid sequence (SEQ ID NO:74) derived from the coding sequence of SEQ ID NO:73 shown in Figure 73.

Figure 75 shows a nucleotide sequence (SEQ ID NO:75) of a native sequence PRO7261 cDNA, wherein SEQ ID NO:75 is a clone designated herein as "DNA49149".

Figure 76 shows the amino acid sequence (SEQ ID NO:76) derived from the coding sequence of SEQ ID NO:75 shown in Figure 75.

Figure 77 shows a nucleotide sequence (SEQ ID NO:77) of a native sequence PRO533 cDNA, wherein SEQ ID NO:77 is a clone designated herein as "DNA49435-1219".

Figure 78 shows the amino acid sequence (SEQ ID NO:78) derived from the coding sequence of SEQ ID NO:77 shown in Figure 77.

Figure 79 shows a nucleotide sequence (SEQ ID NO:79) of a native sequence PRO724 cDNA, wherein SEQ ID NO:79 is a clone designated herein as "DNA49631-1328".

Figure 80 shows the amino acid sequence (SEQ ID NO:80) derived from the coding sequence of SEQ ID NO:79 shown in Figure 79.

Figure 81 shows a nucleotide sequence (SEQ ID NO:81) of a native sequence PRO734 cDNA, wherein SEQ ID NO:81 is a clone designated herein as "DNA49817".

Figure 82 shows the amino acid sequence (SEQ ID NO:82) derived from the coding sequence of SEQ ID NO:81 shown in Figure 81.

Figure 83 shows a nucleotide sequence (SEQ ID NO:83) of a native sequence PRO771 cDNA, wherein SEQ ID NO:83 is a clone designated herein as "DNA49829-1346".

Figure 84 shows the amino acid sequence (SEQ ID NO:84) derived from the coding sequence of SEQ ID

NO:83 shown in Figure 83.

Figure 85 shows a nucleotide sequence (SEQ ID NO:85) of a native sequence PRO2010 cDNA, wherein SEQ ID NO:85 is a clone designated herein as "DNA50792".

Figure 86 shows the amino acid sequence (SEQ ID NO:86) derived from the coding sequence of SEQ ID NO:85 shown in Figure 85.

Figure 87 shows a nucleotide sequence (SEQ ID NO:87) of a native sequence PRO871 cDNA, wherein SEQ ID NO:87 is a clone designated herein as "DNA50919-1361".

Figure 88 shows the amino acid sequence (SEQ ID NO:88) derived from the coding sequence of SEQ ID NO:87 shown in Figure 87.

Figure 89 shows a nucleotide sequence (SEQ ID NO:89) of a native sequence PRO697 cDNA, wherein SEQ ID NO:89 is a clone designated herein as "DNA50920-1325".

Figure 90 shows the amino acid sequence (SEQ ID NO:90) derived from the coding sequence of SEQ ID NO:89 shown in Figure 89.

Figure 91 shows a nucleotide sequence (SEQ ID NO:91) of a native sequence PRO1083 cDNA, wherein SEQ ID NO:91 is a clone designated herein as "DNA50921-1458".

Figure 92 shows the amino acid sequence (SEQ ID NO:22) derived from the coding sequence of SEQ ID NO:91 shown in Figure 91.

Figure 93 shows a nucleotide sequence (SEQ ID NO:93) of a native sequence PRO725 cDNA, wherein SEQ ID NO:93 is a clone designated herein as "DNA52758-1399".

Figure 94 shows the amino acid sequence (SEQ ID NO:94) derived from the coding sequence of SEQ ID NO:93 shown in Figure 93.

Figure 95 shows a nucleotide sequence (SEQ ID NO:95) of a native sequence PRO720 cDNA, wherein SEQ ID NO:95 is a clone designated herein as "DNA53517-1366-1".

Figure 96 shows the amino acid sequence (SEQ ID NO:96) derived from the coding sequence of SEQ ID NO:95 shown in Figure 95.

Figure 97 shows a nucleotide sequence (SEQ ID NO:97) of a native sequence PRO738 cDNA, wherein SEQ ID NO:97 is a clone designated herein as "DNA53915-1258".

Figure 98 shows the amino acid sequence (SEQ ID NO:98) derived from the coding sequence of SEQ ID NO:97 shown in Figure 97.

Figure 99 shows a nucleotide sequence (SEQ ID NO:99) of a native sequence PRO865 cDNA, wherein SEQ ID NO:99 is a clone designated herein as "DNA53974-1401".

Figure 100 shows the amino acid sequence (SEQ ID NO:100) derived from the coding sequence of SEQ ID NO:99 shown in Figure 99.

Figure 101 shows a nucleotide sequence (SEQ ID NO:101) of a native sequence PRO840 cDNA, wherein SEQ ID NO:101 is a clone designated herein as "DNA53987-1438".

Figure 102 shows the amino acid sequence (SEQ ID NO:102) derived from the coding sequence of SEQ ID NO:101 shown in Figure 101.

Figure 103 shows a nucleotide sequence (SEQ ID NO:103) of a native sequence PRO1080 cDNA, wherein SEQ ID NO:103 is a clone designated herein as "DNA56047-1456".

Figure 104 shows the amino acid sequence (SEQ ID NO:104) derived from the coding sequence of SEQ ID NO:103 shown in Figure 103.

Figure 105 shows a nucleotide sequence (SEQ ID NO:105) of a native sequence PRO1079 cDNA, wherein SEQ ID NO:105 is a clone designated herein as "DNA56050-1455".

Figure 106 shows the amino acid sequence (SEQ ID NO:106) derived from the coding sequence of SEQ ID NO:105 shown in Figure 105.

Figure 107 shows a nucleotide sequence (SEQ ID NO:107) of a native sequence PRO793 cDNA, wherein SEQ ID NO:107 is a clone designated herein as "DNA56110-1437".

Figure 108 shows the amino acid sequence (SEQ ID NO:108) derived from the coding sequence of SEQ ID NO:107 shown in Figure 107.

Figure 109 shows a nucleotide sequence (SEQ ID NO:109) of a native sequence PRO788 cDNA, wherein SEQ ID NO:109 is a clone designated herein as "DNA56405-1357".

Figure 110 shows the amino acid sequence (SEQ ID NO:110) derived from the coding sequence of SEQ ID NO:109 shown in Figure 109.

Figure 111 shows a nucleotide sequence (SEQ ID NO:111) of a native sequence PRO938 cDNA, wherein SEQ ID NO:111 is a clone designated herein as "DNA56433-1406".

Figure 112 shows the amino acid sequence (SEQ ID NO:112) derived from the coding sequence of SEQ ID NO:111 shown in Figure 111.

Figure 113 shows a nucleotide sequence (SEQ ID NO:113) of a native sequence PRO1012 cDNA, wherein SEQ ID NO:113 is a clone designated herein as "DNA56439-1376".

Figure 114 shows the amino acid sequence (SEQ ID NO:114) derived from the coding sequence of SEQ ID NO:113 shown in Figure 113.

Figure 115 shows a nucleotide sequence (SEQ ID NO:115) of a native sequence PRO1477 cDNA, wherein SEQ ID NO:115 is a clone designated herein as "DNA56529-1647".

Figure 116 shows the amino acid sequence (SEQ ID NO:116) derived from the coding sequence of SEQ ID NO:115 shown in Figure 115.

Figure 117 shows a nucleotide sequence (SEQ ID NO:117) of a native sequence PRO1134 cDNA, wherein SEQ ID NO:117 is a clone designated herein as "DNA56865-1491".

Figure 118 shows the amino acid sequence (SEQ ID NO:118) derived from the coding sequence of SEQ ID NO:117 shown in Figure 117.

Figure 119 shows a nucleotide sequence (SEQ ID NO:119) of a native sequence PRO162 cDNA, wherein SEQ ID NO:119 is a clone designated herein as "DNA56965-1356".

Figure 120 shows the amino acid sequence (SEQ ID NO:120) derived from the coding sequence of SEQ ID NO:119 shown in Figure 119.

Figure 121 shows a nucleotide sequence (SEQ ID NO:121) of a native sequence PRO1114 cDNA, wherein

SEQ ID NO:121 is a clone designated herein as "DNA57033-1403-1".

Figure 122 shows the amino acid sequence (SEQ ID NO:122) derived from the coding sequence of SEQ ID NO:121 shown in Figure 121.

Figure 123 shows a nucleotide sequence (SEQ ID NO:123) of a native sequence PRO828 cDNA, wherein SEQ ID NO:123 is a clone designated herein as "DNA57037-1444".

Figure 124 shows the amino acid sequence (SEQ ID NO:124) derived from the coding sequence of SEQ ID NO:123 shown in Figure 123.

Figure 125 shows a nucleotide sequence (SEQ ID NO:125) of a native sequence PRO827 cDNA, wherein SEQ ID NO:125 is a clone designated herein as "DNA57039-1402".

Figure 126 shows the amino acid sequence (SEQ ID NO:126) derived from the coding sequence of SEQ ID NO:125 shown in Figure 125.

Figure 127 shows a nucleotide sequence (SEQ ID NO:127) of a native sequence PRO1075 cDNA, wherein SEQ ID NO:127 is a clone designated herein as "DNA57689-1385".

Figure 128 shows the amino acid sequence (SEQ ID NO:128) derived from the coding sequence of SEQ ID NO:127 shown in Figure 127.

Figure 129 shows a nucleotide sequence (SEQ ID NO:129) of a native sequence PRO1007 cDNA, wherein SEQ ID NO:129 is a clone designated herein as "DNA57690-1374".

Figure 130 shows the amino acid sequence (SEQ ID NO:130) derived from the coding sequence of SEQ ID NO:129 shown in Figure 129.

Figure 131 shows a nucleotide sequence (SEQ ID NO:131) of a native sequence PRO826 cDNA, wherein SEQ ID NO:131 is a clone designated herein as "DNA57694-1341".

Figure 132 shows the amino acid sequence (SEQ ID NO:132) derived from the coding sequence of SEQ ID NO:131 shown in Figure 131.

Figure 133 shows a nucleotide sequence (SEQ ID NO:133) of a native sequence PRO819 cDNA, wherein SEQ ID NO:132 is a clone designated herein as "DNA57695-1340".

Figure 134 shows the amino acid sequence (SEQ ID NO:134) derived from the coding sequence of SEQ ID NO:133 shown in Figure 133.

Figure 135 shows a nucleotide sequence (SEQ ID NO:135) of a native sequence PRO1006 cDNA, wherein SEQ ID NO:135 is a clone designated herein as "DNA57699-1412".

Figure 136 shows the amino acid sequence (SEQ ID NO:136) derived from the coding sequence of SEQ ID NO:135 shown in Figure 135.

Figure 137 shows a nucleotide sequence (SEQ ID NO:137) of a native sequence PRO982 cDNA, wherein SEQ ID NO:137 is a clone designated herein as "DNA57700-1408".

Figure 138 shows the amino acid sequence (SEQ ID NO:138) derived from the coding sequence of SEQ ID NO:137 shown in Figure 137.

Figure 139 shows a nucleotide sequence (SEQ ID NO:139) of a native sequence PRO1005 cDNA, wherein SEQ ID NO:139 is a clone designated herein as "DNA57708-1411".

Figure 140 shows the amino acid sequence (SEQ ID NO:140) derived from the coding sequence of SEQ ID NO:139 shown in Figure 139.

Figure 141 shows a nucleotide sequence (SEQ ID NO:141) of a native sequence PRO791 cDNA, wherein SEQ ID NO:141 is a clone designated herein as "DNA57838-1337".

Figure 142 shows the amino acid sequence (SEQ ID NO:142) derived from the coding sequence of SEQ ID NO:141 shown in Figure 141.

Figure 143 shows a nucleotide sequence (SEQ ID NO:143) of a native sequence PRO1071 cDNA, wherein SEQ ID NO:143 is a clone designated herein as "DNA58847-1383".

Figure 144 shows the amino acid sequence (SEQ ID NO:144) derived from the coding sequence of SEQ ID NO:143 shown in Figure 43.

Figure 145 shows a nucleotide sequence (SEQ ID NO:145) of a native sequence PRO1415 cDNA, wherein SEQ ID NO:145 is a clone designated herein as "DNA58852-1637".

Figure 146 shows the amino acid sequence (SEQ ID NO:146) derived from the coding sequence of SEQ ID NO:145 shown in Figure 145.

Figure 147 shows a nucleotide sequence (SEQ ID NO:147) of a native sequence PRO1054 cDNA, wherein SEQ ID NO:147 is a clone designated herein as "DNA58853-1423".

Figure 148 shows the amino acid sequence (SEQ ID NO:148) derived from the coding sequence of SEQ ID NO:147 shown in Figure 147.

Figure 149 shows a nucleotide sequence (SEQ ID NO:149) of a native sequence PRO1411 cDNA, wherein SEQ ID NO:149 is a clone designated herein as "DNA59212-1627".

Figure 150 shows the amino acid sequence (SEQ ID NO:150) derived from the coding sequence of SEQ ID NO:149 shown in Figure 149.

Figure 151 shows a nucleotide sequence (SEQ ID NO:151) of a native sequence PRO1184 cDNA, wherein SEQ ID NO:151 is a clone designated herein as "DNA59220-1514".

Figure 152 shows the amino acid sequence (SEQ ID NO:152) derived from the coding sequence of SEQ ID NO:151 shown in Figure 151.

Figure 153 shows a nucleotide sequence (SEQ ID NO:153) of a native sequence PRO1029 cDNA, wherein SEQ ID NO:153 is a clone designated herein as "DNA59493-1420".

Figure 154 shows the amino acid sequence (SEQ ID NO:154) derived from the coding sequence of SEQ ID NO:153 shown in Figure 153.

Figure 155 shows a nucleotide sequence (SEQ ID NO:155) of a native sequence PRO1139 cDNA, wherein SEQ ID NO:155 is a clone designated herein as "DNA59497-1496".

Figure 156 shows the amino acid sequence (SEQ ID NO:156) derived from the coding sequence of SEQ ID NO:155 shown in Figure 155.

Figure 157 shows a nucleotide sequence (SEQ ID NO:157) of a native sequence PRO1190 cDNA, wherein SEQ ID NO:157 is a clone designated herein as "DNA59586-1520".

Figure 158 shows the amino acid sequence (SEQ ID NO:158) derived from the coding sequence of SEQ

ID NO:157 shown in Figure 157.

Figure 159 shows a nucleotide sequence (SEQ ID NO:159) of a native sequence PRO1309 cDNA, wherein SEQ ID NO:159 is a clone designated herein as "DNA59588-1571".

Figure 160 shows the amino acid sequence (SEQ ID NO:160) derived from the coding sequence of SEQ ID NO:159 shown in Figure 159.

Figure 161 shows a nucleotide sequence (SEQ ID NO:161) of a native sequence PRO836 cDNA, wherein SEQ ID NO:161 is a clone designated herein as "DNA59620-1463".

Figure 162 shows the amino acid sequence (SEQ ID NO:162) derived from the coding sequence of SEQ ID NO:161 shown in Figure 161.

Figure 163 shows a nucleotide sequence (SEQ ID NO:163) of a native sequence PRO1025 cDNA, wherein SEQ ID NO:163 is a clone designated herein as "DNA59622-1334".

Figure 164 shows the amino acid sequence (SEQ ID NO:164) derived from the coding sequence of SEQ ID NO:163 shown in Figure 163.

Figure 165 shows a nucleotide sequence (SEQ ID NO:165) of a native sequence PRO1131 cDNA, wherein SEQ ID NO:165 is a clone designated herein as "DNA59777-1480".

Figure 166 shows the amino acid sequence (SEQ ID NO:166) derived from the coding sequence of SEQ ID NO:165 shown in Figure 165.

Figure 167 shows a nucleotide sequence (SEQ ID NO:167) of a native sequence PRO1182 cDNA, wherein SEQ ID NO:167 is a clone designated herein as "DNA59848-1512".

Figure 168 shows the amino acid sequence (SEQ ID NO:168) derived from the coding sequence of SEQ ID NO:167 shown in Figure 167.

Figure 169 shows a nucleotide sequence (SEQ ID NO:169) of a native sequence PRO1155 cDNA, wherein SEQ ID NO:169 is a clone designated herein as "DNA59849-1504".

Figure 170 shows the amino acid sequence (SEQ ID NO:170) derived from the coding sequence of SEQ ID NO:169 shown in Figure 169.

Figure 171 shows a nucleotide sequence (SEQ ID NO:171) of a native sequence PRO1186 cDNA, wherein SEQ ID NO:171 is a clone designated herein as "DNA60621-1516".

Figure 172 shows the amino acid sequence (SEQ ID NO:172) derived from the coding sequence of SEQ ID NO:171 shown in Figure 171.

Figure 173 shows a nucleotide sequence (SEQ ID NO:173) of a native sequence PRO1198 cDNA, wherein SEQ ID NO:173 is a clone designated herein as "DNA60622-1525".

Figure 174 shows the amino acid sequence (SEQ ID NO:174) derived from the coding sequence of SEQ ID NO:173 shown in Figure 173.

Figure 175 shows a nucleotide sequence (SEQ ID NO:175) of a native sequence PRO1265 cDNA, wherein SEQ ID NO:175 is a clone designated herein as "DNA60764-1533".

Figure 176 shows the amino acid sequence (SEQ ID NO:176) derived from the coding sequence of SEQ ID NO:175 shown in Figure 175.

Figure 177 shows a nucleotide sequence (SEQ ID NO:177) of a native sequence PRO1361 cDNA, wherein SEQ ID NO:177 is a clone designated herein as "DNA60783-1611".

Figure 178 shows the amino acid sequence (SEQ ID NO:178) derived from the coding sequence of SEQ ID NO:177 shown in Figure 177.

Figure 179 shows a nucleotide sequence (SEQ ID NO:179) of a native sequence PRO1287 cDNA, wherein SEQ ID NO:179 is a clone designated herein as "DNA61755-1554".

Figure 180 shows the amino acid sequence (SEQ ID NO:180) derived from the coding sequence of SEQ ID NO:179 shown in Figure 179.

Figure 181 shows a nucleotide sequence (SEQ ID NO:181) of a native sequence PRO1308 cDNA, wherein SEQ ID NO:181 is a clone designated herein as "DNA62306-1570".

Figure 182 shows the amino acid sequence (SEQ ID NO:182) derived from the coding sequence of SEQ ID NO:181 shown in Figure 181.

Figure 183 shows a nucleotide sequence (SEQ ID NO:183) of a native sequence PRO4313 cDNA, wherein SEQ ID NO:183 is a clone designated herein as "DNA62312-2558".

Figure 184 shows the amino acid sequence (SEQ ID NO:184) derived from the coding sequence of SEQ ID NO:183 shown in Figure 183.

Figure 185 shows a nucleotide sequence (SEQ ID NO:185) of a native sequence PRO1192 cDNA, wherein SEQ ID NO:185 is a clone designated herein as "DNA62814-1521".

Figure 186 shows the amino acid sequence (SEQ ID NO:186) derived from the coding sequence of SEQ ID NO:185 shown in Figure 185.

Figure 187 shows a nucleotide sequence (SEQ ID NO:187) of a native sequence PRO1160 cDNA, wherein SEQ ID NO:187 is a clone designated herein as "DNA62872-1509".

Figure 188 shows the amino acid sequence (SEQ ID NO:188) derived from the coding sequence of SEQ ID NO:187 shown in Figure 187.

Figure 189 shows a nucleotide sequence (SEQ ID NO:189) of a native sequence PRO1244 cDNA, wherein SEQ ID NO:189 is a clone designated herein as "DNA64883-1526".

Figure 190 shows the amino acid sequence (SEQ ID NO:190) derived from the coding sequence of SEQ ID NO:189 shown in Figure 189.

Figure 191 shows a nucleotide sequence (SEQ ID NO:191) of a native sequence PRO1356 cDNA, wherein SEQ ID NO:191 is a clone designated herein as "DNA64886-1601".

Figure 192 shows the amino acid sequence (SEQ ID NO:192) derived from the coding sequence of SEQ ID NO:191 shown in Figure 191.

Figure 193 shows a nucleotide sequence (SEQ ID NO:193) of a native sequence PRO1274 cDNA, wherein SEQ ID NO:193 is a clone designated herein as "DNA64889-1541".

Figure 194 shows the amino acid sequence (SEQ ID NO:194) derived from the coding sequence of SEQ ID NO:193 shown in Figure 193.

Figure 195 shows a nucleotide sequence (SEQ ID NO:195) of a native sequence PRO1272 cDNA, wherein

SEQ ID NO:195 is a clone designated herein as "DNA64896-1539".

Figure 196 shows the amino acid sequence (SEQ ID NO:196) derived from the coding sequence of SEQ ID NO:195 shown in Figure 195.

Figure 197 shows a nucleotide sequence (SEQ ID NO:197) of a native sequence PRO1412 cDNA, wherein SEQ ID NO:197 is a clone designated herein as "DNA64897-1628".

Figure 198 shows the amino acid sequence (SEQ ID NO:198) derived from the coding sequence of SEQ ID NO:197 shown in Figure 197.

Figure 199 shows a nucleotide sequence (SEQ ID NO:199) of a native sequence PRO1286 cDNA, wherein SEQ ID NO:199 is a clone designated herein as "DNA64903-1553".

Figure 200 shows the amino acid sequence (SEQ ID NO:200) derived from the coding sequence of SEQ ID NO:199 shown in Figure 199.

Figure 201 shows a nucleotide sequence (SEQ ID NO:201) of a native sequence PRO1347 cDNA, wherein SEQ ID NO:201 is a clone designated herein as "DNA64950-1590".

Figure 202 shows the amino acid sequence (SEQ ID NO:202) derived from the coding sequence of SEQ ID NO:201 shown in Figure 201.

Figure 203 shows a nucleotide sequence (SEQ ID NO:203) of a native sequence PRO1273 cDNA, wherein SEQ ID NO:203 is a clone designated herein as "DNA65402-1540".

Figure 204 shows the amino acid sequence (SEQ ID NO:204) derived from the coding sequence of SEQ ID NO:203 shown in Figure 203.

Figure 205 shows a nucleotide sequence (SEQ ID NO:205) of a native sequence PRO1283 cDNA, wherein SEQ ID NO:205 is a clone designated herein as "DNA65404-1551".

Figure 206 shows the amino acid sequence (SEQ ID NO:206) derived from the coding sequence of SEQ ID NO:205 shown in Figure 205.

Figure 207 shows a nucleotide sequence (SEQ ID NO:207) of a native sequence PRO1279 cDNA, wherein SEQ ID NO:207 is a clone designated herein as "DNA65405-1547".

Figure 208 shows the amino acid sequence (SEQ ID NO:208) derived from the coding sequence of SEQ ID NO:207 shown in Figure 207.

Figure 209 shows a nucleotide sequence (SEQ ID NO:209) of a native sequence PRO1306 cDNA, wherein SEQ ID NO:209 is a clone designated herein as "DNA65410-1569".

Figure 210 shows the amino acid sequence (SEQ ID NO:210) derived from the coding sequence of SEQ ID NO:209 shown in Figure 209.

Figure 211 shows a nucleotide sequence (SEQ ID NO:211) of a native sequence PRO1195 cDNA, wherein SEQ ID NO:211 is a clone designated herein as "DNA65412-1523".

Figure 212 shows the amino acid sequence (SEQ ID NO:212) derived from the coding sequence of SEQ ID NO:211 shown in Figure 211.

Figure 213 shows a nucleotide sequence (SEQ ID NO:213) of a native sequence PRO4995 cDNA, wherein SEQ ID NO:213 is a clone designated herein as "DNA66307-2661".

Figure 214 shows the amino acid sequence (SEQ ID NO:214) derived from the coding sequence of SEQ ID NO:213 shown in Figure 213.

Figure 215 shows a nucleotide sequence (SEQ ID NO:215) of a native sequence PRO1382 cDNA, wherein SEQ ID NO:215 is a clone designated herein as "DNA66526-1616".

Figure 216 shows the amino acid sequence (SEQ ID NO:216) derived from the coding sequence of SEQ ID NO:215 shown in Figure 215.

Figure 217 shows a nucleotide sequence (SEQ ID NO:217) of a native sequence PRO1325 cDNA, wherein SEQ ID NO:217 is a clone designated herein as "DNA66659-1593".

Figure 218 shows the amino acid sequence (SEQ ID NO:218) derived from the coding sequence of SEQ ID NO:217 shown in Figure 217.

Figure 219 shows a nucleotide sequence (SEQ ID NO:219) of a native sequence PRO1329 cDNA, wherein SEQ ID NO:219 is a clone designated herein as "DNA66660-1585".

Figure 220 shows the amino acid sequence (SEQ ID NO:220) derived from the coding sequence of SEQ ID NO:219 shown in Figure 219.

Figure 221 shows a nucleotide sequence (SEQ ID NO:221) of a native sequence PRO1338 cDNA, wherein SEQ ID NO:221 is a clone designated herein as "DNA66667-1596".

Figure 222 shows the amino acid sequence (SEQ ID NO:222) derived from the coding sequence of SEQ ID NO:221 shown in Figure 221.

Figure 223 shows a nucleotide sequence (SEQ ID NO:223) of a native sequence PRO1337 cDNA, wherein SEQ ID NO:223 is a clone designated herein as "DNA66672-1586".

Figure 224 shows the amino acid sequence (SEQ ID NO:224) derived from the coding sequence of SEQ ID NO:223 shown in Figure 223.

Figure 225 shows a nucleotide sequence (SEQ ID NO:225) of a native sequence PRO1343 cDNA, wherein SEQ ID NO:225 is a clone designated herein as "DNA66675-1587".

Figure 226 shows the amino acid sequence (SEQ ID NO:226) derived from the coding sequence of SEQ ID NO:225 shown in Figure 225.

Figure 227 shows a nucleotide sequence (SEQ ID NO:227) of a native sequence PRO1376 cDNA, wherein SEQ ID NO:227 is a clone designated herein as "DNA67300-1605".

Figure 228 shows the amino acid sequence (SEQ ID NO:228) derived from the coding sequence of SEQ ID NO:227 shown in Figure 227.

Figure 229 shows a nucleotide sequence (SEQ ID NO:229) of a native sequence PRO1434 cDNA, wherein SEQ ID NO:229 is a clone designated herein as "DNA68818-2536".

Figure 230 shows the amino acid sequence (SEQ ID NO:230) derived from the coding sequence of SEQ ID NO:229 shown in Figure 229.

Figure 231 shows a nucleotide sequence (SEQ ID NO:231) of a native sequence PRO3579 cDNA, wherein SEQ ID NO:231 is a clone designated herein as "DNA68862-2546".

Figure 232 shows the amino acid sequence (SEQ ID NO:232) derived from the coding sequence of SEQ

ID NO:231 shown in Figure 231.

Figure 233 shows a nucleotide sequence (SEQ ID NO:233) of a native sequence PRO1387 cDNA, wherein SEQ ID NO:233 is a clone designated herein as "DNA68872-1620".

Figure 234 shows the amino acid sequence (SEQ ID NO:234) derived from the coding sequence of SEQ ID NO:233 shown in Figure 233.

Figure 235 shows a nucleotide sequence (SEQ ID NO:235) of a native sequence PRO1419 cDNA, wherein SEQ ID NO:235 is a clone designated herein as "DNA71290-1630".

Figure 236 shows the amino acid sequence (SEQ ID NO:236) derived from the coding sequence of SEQ ID NO:235 shown in Figure 235.

Figure 237 shows a nucleotide sequence (SEQ ID NO:237) of a native sequence PRO1488 cDNA, wherein SEQ ID NO:237 is a clone designated herein as "DNA73736-1657".

Figure 238 shows the amino acid sequence (SEQ ID NO:238) derived from the coding sequence of SEQ ID NO:237 shown in Figure 237.

Figure 239 shows a nucleotide sequence (SEQ ID NO:239) of a native sequence PRO1474 cDNA, wherein SEQ ID NO:239 is a clone designated herein as "DNA73739-1645".

Figure 240 shows the amino acid sequence (SEQ ID NO:240) derived from the coding sequence of SEQ ID NO:239 shown in Figure 239.

Figure 241 shows a nucleotide sequence (SEQ ID NO:241) of a native sequence PRO1508 cDNA, wherein SEQ ID NO:241 is a clone designated herein as "DNA73742-1662".

Figure 242 shows the amino acid sequence (SEQ ID NO:242) derived from the coding sequence of SEQ ID NO:241 shown in Figure 241.

Figure 243 shows a nucleotide sequence (SEQ ID NO:243) of a native sequence PRO1754 cDNA, wherein SEQ ID NO:243 is a clone designated herein as "DNA76385-1692".

Figure 244 shows the amino acid sequence (SEQ ID NO:244) derived from the coding sequence of SEQ ID NO:243 shown in Figure 243.

Figure 245 shows a nucleotide sequence (SEQ ID NO:245) of a native sequence PRO1550 cDNA, wherein SEQ ID NO:245 is a clone designated herein as "DNA76393-1664".

Figure 246 shows the amino acid sequence (SEQ ID NO:246) derived from the coding sequence of SEQ ID NO:245 shown in Figure 245.

Figure 247 shows a nucleotide sequence (SEQ ID NO:247) of a native sequence PRO1758 cDNA, wherein SEQ ID NO:247 is a clone designated herein as "DNA76399-1700".

Figure 248 shows the amino acid sequence (SEQ ID NO:248) derived from the coding sequence of SEQ ID NO:247 shown in Figure 247.

Figure 249 shows a nucleotide sequence (SEQ ID NO:249) of a native sequence PRO1917 cDNA, wherein SEQ ID NO:249 is a clone designated herein as "DNA76400-2528".

Figure 250 shows the amino acid sequence (SEQ ID NO:250) derived from the coding sequence of SEQ ID NO:249 shown in Figure 249.

Figure 251 shows a nucleotide sequence (SEQ ID NO:251) of a native sequence PRO1787 cDNA, wherein SEQ ID NO:251 is a clone designated herein as "DNA76510-2504".

Figure 252 shows the amino acid sequence (SEQ ID NO:252) derived from the coding sequence of SEQ ID NO:251 shown in Figure 251.

Figure 253 shows a nucleotide sequence (SEQ ID NO:253) of a native sequence PRO1556 cDNA, wherein SEQ ID NO:253 is a clone designated herein as "DNA76529-1666".

Figure 254 shows the amino acid sequence (SEQ ID NO:254) derived from the coding sequence of SEQ ID NO:253 shown in Figure 253.

Figure 255 shows a nucleotide sequence (SEQ ID NO:255) of a native sequence PRO1760 cDNA, wherein SEQ ID NO:255 is a clone designated herein as "DNA76532-1702".

Figure 256 shows the amino acid sequence (SEQ ID NO:256) derived from the coding sequence of SEQ ID NO:255 shown in Figure 255.

Figure 257 shows a nucleotide sequence (SEQ ID NO:257) of a native sequence PRO1567 cDNA, wherein SEQ ID NO:257 is a clone designated herein as "DNA76541-1675".

Figure 258 shows the amino acid sequence (SEQ ID NO:258) derived from the coding sequence of SEQ ID NO:257 shown in Figure 257.

Figure 259 shows a nucleotide sequence (SEQ ID NO:259) of a native sequence PRO1600 cDNA, wherein SEQ ID NO:259 is a clone designated herein as "DNA77503-1686".

Figure 260 shows the amino acid sequence (SEQ ID NO:260) derived from the coding sequence of SEQ ID NO:259 shown in Figure 259.

Figure 261 shows a nucleotide sequence (SEQ ID NO:261) of a native sequence PRO1868 cDNA, wherein SEQ ID NO:261 is a clone designated herein as "DNA77624-2515".

Figure 262 shows the amino acid sequence (SEQ ID NO:262) derived from the coding sequence of SEQ ID NO:261 shown in Figure 261.

Figure 263 shows a nucleotide sequence (SEQ ID NO:263) of a native sequence PRO1890 cDNA, wherein SEQ ID NO:263 is a clone designated herein as "DNA79230-2525".

Figure 264 shows the amino acid sequence (SEQ ID NO:264) derived from the coding sequence of SEQ ID NO:263 shown in Figure 263.

Figure 265 shows a nucleotide sequence (SEQ ID NO:265) of a native sequence PRO1887 cDNA, wherein SEQ ID NO:265 is a clone designated herein as "DNA79862-2522".

Figure 266 shows the amino acid sequence (SEQ ID NO:265) derived from the coding sequence of SEQ ID NO:265 shown in Figure 265.

Figure 267 shows a nucleotide sequence (SEQ ID NO:267) of a native sequence PRO4353 cDNA, wherein SEQ ID NO:267 is a clone designated herein as "DNA80145-2594".

Figure 268 shows the amino acid sequence (SEQ ID NO:268) derived from the coding sequence of SEQ ID NO:267 shown in Figure 267.

Figure 269 shows a nucleotide sequence (SEQ ID NO:269) of a native sequence PRO1782 cDNA, wherein

SEQ ID NO:269 is a clone designated herein as "DNA80899-2501".

Figure 270 shows the amino acid sequence (SEQ ID NO:270) derived from the coding sequence of SEQ ID NO:269 shown in Figure 269.

Figure 271 shows a nucleotide sequence (SEQ ID NO:271) of a native sequence PRO1928 cDNA, wherein SEQ ID NO:271 is a clone designated herein as "DNA81754-2532".

Figure 272 shows the amino acid sequence (SEQ ID NO:272) derived from the coding sequence of SEQ ID NO:271 shown in Figure 271.

Figure 273 shows a nucleotide sequence (SEQ ID NO:273) of a native sequence PRO1865 cDNA, wherein SEQ ID NO:273 is a clone designated herein as "DNA81757-2512".

Figure 274 shows the amino acid sequence (SEQ ID NO:274) derived from the coding sequence of SEQ ID NO:273 shown in Figure 273.

Figure 275 shows a nucleotide sequence (SEQ ID NO:275) of a native sequence PRO4341 cDNA, wherein SEQ ID NO:275 is a clone designated herein as "DNA81761-2583".

Figure 276 shows the amino acid sequence (SEQ ID NO:276) derived from the coding sequence of SEQ ID NO:275 shown in Figure 275.

Figure 277 shows a nucleotide sequence (SEQ ID NO:277) of a native sequence PRO6714 cDNA, wherein SEQ ID NO:277 is a clone designated herein as "DNA82358-2738".

Figure 278 shows the amino acid sequence (SEQ ID NO:278) derived from the coding sequence of SEQ ID NO:277 shown in Figure 277.

Figure 279 shows a nucleotide sequence (SEQ ID NO:279) of a native sequence PRO5723 cDNA, wherein SEQ ID NO:279 is a clone designated herein as "DNA82361".

Figure 280 shows the amino acid sequence (SEQ ID NO:280) derived from the coding sequence of SEQ ID NO:279 shown in Figure 279.

Figure 281 shows a nucleotide sequence (SEQ ID NO:281) of a native sequence PRO3438 cDNA, wherein SEQ ID NO:281 is a clone designated herein as "DNA82364-2538".

Figure 282 shows the amino acid sequence (SEQ ID NO:282) derived from the coding sequence of SEQ ID NO:281 shown in Figure 281.

Figure 283 shows a nucleotide sequence (SEQ ID NO:283) of a native sequence PRO6071 cDNA, wherein SEQ ID NO:283 is a clone designated herein as "DNA82403-2959".

Figure 284 shows the amino acid sequence (SEQ ID NO:284) derived from the coding sequence of SEQ ID NO:283 shown in Figure 283.

Figure 285 shows a nucleotide sequence (SEQ ID NO:285) of a native sequence PRO1801 cDNA, wherein SEQ ID NO:285 is a clone designated herein as "DNA83500-2506".

Figure 286 shows the amino acid sequence (SEQ ID NO:286) derived from the coding sequence of SEQ ID NO:285 shown in Figure 285.

Figure 287 shows a nucleotide sequence (SEQ ID NO:287) of a native sequence PRO4324 cDNA, wherein SEQ ID NO:287 is a clone designated herein as "DNA83560-2569".

Figure 288 shows the amino acid sequence (SEQ ID NO:288) derived from the coding sequence of SEQ ID NO:287 shown in Figure 287.

Figure 289 shows a nucleotide sequence (SEQ ID NO:289) of a native sequence PRO4333 cDNA, wherein SEQ ID NO:289 is a clone designated herein as "DNA84210-2576".

Figure 290 shows the amino acid sequence (SEQ ID NO:290) derived from the coding sequence of SEQ ID NO:289 shown in Figure 289.

Figure 291 shows a nucleotide sequence (SEQ ID NO:291) of a native sequence PRO4405 cDNA, wherein SEQ ID NO:291 is a clone designated herein as "DNA84920-2614".

Figure 292 shows the amino acid sequence (SEQ ID NO:292) derived from the coding sequence of SEQ ID NO:291 shown in Figure 291.

Figure 293 shows a nucleotide sequence (SEQ ID NO:293) of a native sequence PRO4356 cDNA, wherein SEQ ID NO:293 is a clone designated herein as "DNA86576-2595".

Figure 294 shows the amino acid sequence (SEQ ID NO:294) derived from the coding sequence of SEQ ID NO:293 shown in Figure 293.

Figure 295 shows a nucleotide sequence (SEQ ID NO:295) of a native sequence PRO3444 cDNA, wherein SEQ ID NO:295 is a clone designated herein as "DNA87997".

Figure 296 shows the amino acid sequence (SEQ ID NO:296) derived from the coding sequence of SEQ ID NO:295 shown in Figure 295.

Figure 297 shows a nucleotide sequence (SEQ ID NO:297) of a native sequence PRO4302 cDNA, wherein SEQ ID NO:297 is a clone designated herein as "DNA92218-2554".

Figure 298 shows the amino acid sequence (SEQ ID NO:298) derived from the coding sequence of SEQ ID NO:297 shown in Figure 297.

Figure 299 shows a nucleotide sequence (SEQ ID NO:299) of a native sequence PRO4371 cDNA, wherein SEQ ID NO:299 is a clone designated herein as "DNA92233-2599".

Figure 300 shows the amino acid sequence (SEQ ID NO:300) derived from the coding sequence of SEQ ID NO:299 shown in Figure 299.

Figure 301 shows a nucleotide sequence (SEQ ID NO:301) of a native sequence PRO4354 cDNA, wherein SEQ ID NO:301 is a clone designated herein as "DNA92256-2596".

Figure 302 shows the amino acid sequence (SEQ ID NO:302) derived from the coding sequence of SEQ ID NO:301 shown in Figure 301.

Figure 303 shows a nucleotide sequence (SEQ ID NO:303) of a native sequence PRO5725 cDNA, wherein SEQ ID NO:303 is a clone designated herein as "DNA92265-2669".

Figure 304 shows the amino acid sequence (SEQ ID NO:304) derived from the coding sequence of SEQ ID NO:303 shown in Figure 303.

Figure 305 shows a nucleotide sequence (SEQ ID NO:305) of a native sequence PRO4408 cDNA, wherein SEQ ID NO:305 is a clone designated herein as "DNA92274-2617".

Figure 306 shows the amino acid sequence (SEQ ID NO:306) derived from the coding sequence of SEQ

ID NO:305 shown in Figure 305.

Figure 307 shows a nucleotide sequence (SEQ ID NO:307) of a native sequence PRO9940 cDNA, wherein SEQ ID NO:307 is a clone designated herein as "DNA92282".

Figure 308 shows the amino acid sequence (SEQ ID NO:308) derived from the coding sequence of SEQ ID NO:307 shown in Figure 307.

Figure 309 shows a nucleotide sequence (SEQ ID NO:309) of a native sequence PRO5737 cDNA, wherein SEQ ID NO:309 is a clone designated herein as "DNA92929-2534-1".

Figure 310 shows the amino acid sequence (SEQ ID NO:310) derived from the coding sequence of SEQ ID NO:309 shown in Figure 309.

Figure 311 shows a nucleotide sequence (SEQ ID NO:311) of a native sequence PRO4425 cDNA, wherein SEQ ID NO:311 is a clone designated herein as "DNA93011-2637".

Figure 312 shows the amino acid sequence (SEQ ID NO:312) derived from the coding sequence of SEQ ID NO:311 shown in Figure 311.

Figure 313 shows a nucleotide sequence (SEQ ID NO:313) of a native sequence PRO4345 cDNA, wherein SEQ ID NO:313 is a clone designated herein as "DNA94854-2586".

Figure 314 shows the amino acid sequence (SEQ ID NO:314) derived from the coding sequence of SEQ ID NO:313 shown in Figure 313.

Figure 315 shows a nucleotide sequence (SEQ ID NO:315) of a native sequence PRO4342 cDNA, wherein SEQ ID NO:315 is a clone designated herein as "DNA96787-2534-1".

Figure 316 shows the amino acid sequence (SEQ ID NO:316) derived from the coding sequence of SEQ ID NO:315 shown in Figure 315.

Figure 317 shows a nucleotide sequence (SEQ ID NO:317) of a native sequence PRO3562 cDNA, wherein SEQ ID NO:317 is a clone designated herein as "DNA96791".

Figure 318 shows the amino acid sequence (SEQ ID NO:318) derived from the coding sequence of SEQ ID NO:317 shown in Figure 317.

Figure 319 shows a nucleotide sequence (SEQ ID NO:319) of a native sequence PRO4422 cDNA, wherein SEQ ID NO:319 is a clone designated herein as "DNA96867-2620".

Figure 320 shows the amino acid sequence (SEQ ID NO:320) derived from the coding sequence of SEQ ID NO:319 shown in Figure 319.

Figure 321 shows a nucleotide sequence (SEQ ID NO:321) of a native sequence PRO5776 cDNA, wherein SEQ ID NO:321 is a clone designated herein as "DNA96872-2674".

Figure 322 shows the amino acid sequence (SEQ ID NO:322) derived from the coding sequence of SEQ ID NO:321 shown in Figure 321.

Figure 323 shows a nucleotide sequence (SEQ ID NO:323) of a native sequence PRO4430 cDNA, wherein SEQ ID NO:323 is a clone designated herein as "DNA96878-2626".

Figure 324 shows the amino acid sequence (SEQ ID NO:324) derived from the coding sequence of SEQ ID NO:323 shown in Figure 323.

Figure 325 shows a nucleotide sequence (SEQ ID NO:325) of a native sequence PRO4499 cDNA, wherein SEQ ID NO:325 is a clone designated herein as "DNA96889-2641".

Figure 326 shows the amino acid sequence (SEQ ID NO:326) derived from the coding sequence of SEQ ID NO:325 shown in Figure 325.

Figure 327 shows a nucleotide sequence (SEQ ID NO:327) of a native sequence PRO4503 cDNA, wherein SEQ ID NO:327 is a clone designated herein as "DNA100312-2645".

Figure 328 shows the amino acid sequence (SEQ ID NO:328) derived from the coding sequence of SEQ ID NO:327 shown in Figure 327.

Figure 329 shows a nucleotide sequence (SEQ ID NO:329) of a native sequence PRO10008 cDNA, wherein SEQ ID NO:329 is a clone designated herein as "DNA101921".

Figure 330 shows the amino acid sequence (SEQ ID NO:330) derived from the coding sequence of SEQ ID NO:329 shown in Figure 329.

Figure 331 shows a nucleotide sequence (SEQ ID NO:331) of a native sequence PRO5730 cDNA, wherein SEQ ID NO:331 is a clone designated herein as "DNA101926".

Figure 332 shows the amino acid sequence (SEQ ID NO:332) derived from the coding sequence of SEQ ID NO:331 shown in Figure 331.

Figure 333 shows a nucleotide sequence (SEQ ID NO:333) of a native sequence PRO6008 cDNA, wherein SEQ ID NO:333 is a clone designated herein as "DNA102844".

Figure 334 shows the amino acid sequence (SEQ ID NO:334) derived from the coding sequence of SEQ ID NO:333 shown in Figure 333.

Figure 335 shows a nucleotide sequence (SEQ ID NO:335) of a native sequence PRO4527 cDNA, wherein SEQ ID NO:335 is a clone designated herein as "DNA103197".

Figure 336 shows the amino acid sequence (SEQ ID NO:336) derived from the coding sequence of SEQ ID NO:335 shown in Figure 335.

Figure 337 shows a nucleotide sequence (SEQ ID NO:337) of a native sequence PRO4538 cDNA, wherein SEQ ID NO:337 is a clone designated herein as "DNA103208".

Figure 338 shows the amino acid sequence (SEQ ID NO:338) derived from the coding sequence of SEQ ID NO:337 shown in Figure 337.

Figure 339 shows a nucleotide sequence (SEQ ID NO:339) of a native sequence PRO4553 cDNA, wherein SEQ ID NO:339 is a clone designated herein as "DNA103223".

Figure 340 shows the amino acid sequence (SEQ ID NO:340) derived from the coding sequence of SEQ ID NO:339 shown in Figure 339.

Figure 341 shows a nucleotide sequence (SEQ ID NO:341) of a native sequence PRO6006 cDNA, wherein SEQ ID NO:341 is a clone designated herein as "DNA105782-2693".

Figure 342 shows the amino acid sequence (SEQ ID NO:342) derived from the coding sequence of SEQ ID NO:341 shown in Figure 341.

Figure 343 shows a nucleotide sequence (SEQ ID NO:343) of a native sequence PRO6029 cDNA, wherein

SEQ ID NO:343 is a clone designated herein as "DNA105849-2704".

Figure 344 shows the amino acid sequence (SEQ ID NO:344) derived from the coding sequence of SEQ ID NO:343 shown in Figure 343.

Figure 345 shows a nucleotide sequence (SEQ ID NO:345) of a native sequence PRO9821 cDNA, wherein SEQ ID NO:345 is a clone designated herein as "DNA108725-2766".

Figure 346 shows the amino acid sequence (SEQ ID NO:346) derived from the coding sequence of SEQ ID NO:345 shown in Figure 345.

Figure 347 shows a nucleotide sequence (SEQ ID NO:347) of a native sequence PRO9820 cDNA, wherein SEQ ID NO:347 is a clone designated herein as "DNA108769-2765".

Figure 348 shows the amino acid sequence (SEQ ID NO:348) derived from the coding sequence of SEQ ID NO:347 shown in Figure 347.

Figure 349 shows a nucleotide sequence (SEQ ID NO:349) of a native sequence PRO9771 cDNA, wherein SEQ ID NO:349 is a clone designated herein as "DNA119498-2965".

Figure 350 shows the amino acid sequence (SEQ ID NO:350) derived from the coding sequence of SEQ ID NO:349 shown in Figure 349.

Figure 351 shows a nucleotide sequence (SEQ ID NO:351) of a native sequence PRO7436 cDNA, wherein SEQ ID NO:351 is a clone designated herein as "DNA119535-2756".

Figure 352 shows the amino acid sequence (SEQ ID NO:352) derived from the coding sequence of SEQ ID NO:351 shown in Figure 351.

Figure 353 shows a nucleotide sequence (SEQ ID NO:353) of a native sequence PRO10096 cDNA, wherein SEQ ID NO:353 is a clone designated herein as "DNA125185-2806".

Figure 354 shows the amino acid sequence (SEQ ID NO:354) derived from the coding sequence of SEQ ID NO:353 shown in Figure 353.

Figure 355 shows a nucleotide sequence (SEQ ID NO:355) of a native sequence PRO19670 cDNA, wherein SEQ ID NO:355 is a clone designated herein as "DNA131639-2874".

Figure 356 shows the amino acid sequence (SEQ ID NO:356) derived from the coding sequence of SEQ ID NO:355 shown in Figure 355.

Figure 357 shows a nucleotide sequence (SEQ ID NO:357) of a native sequence PRO20044 cDNA, wherein SEQ ID NO:357 is a clone designated herein as "DNA139623-2893".

Figure 358 shows the amino acid sequence (SEQ ID NO:358) derived from the coding sequence of SEQ ID NO:357 shown in Figure 357.

Figure 359 shows a nucleotide sequence (SEQ ID NO:359) of a native sequence PRO9873 cDNA, wherein SEQ ID NO:359 is a clone designated herein as "DNA143076-2787".

Figure 360 shows the amino acid sequence (SEQ ID NO:360) derived from the coding sequence of SEQ ID NO:359 shown in Figure 359.

Figure 361 shows a nucleotide sequence (SEQ ID NO:361) of a native sequence PRO21366 cDNA, wherein SEQ ID NO:361 is a clone designated herein as "DNA143276-2975".

Figure 362 shows the amino acid sequence (SEQ ID NO:362) derived from the coding sequence of SEQ ID NO:361 shown in Figure 361.

Figure 363 shows a nucleotide sequence (SEQ ID NO:363) of a native sequence PRO20040 cDNA, wherein SEQ ID NO:363 is a clone designated herein as "DNA164625-2890".

Figure 364 shows the amino acid sequence (SEQ ID NO:364) derived from the coding sequence of SEQ ID NO:363 shown in Figure 363.

Figure 365 shows a nucleotide sequence (SEQ ID NO:365) of a native sequence PRO21184 cDNA, wherein SEQ ID NO:365 is a clone designated herein as "DNA167678-2963".

Figure 366 shows the amino acid sequence (SEQ ID NO:366) derived from the coding sequence of SEQ ID NO:365 shown in Figure 365.

Figure 367 shows a nucleotide sequence (SEQ ID NO:367) of a native sequence PRO21055 cDNA, wherein SEQ ID NO:367 is a clone designated herein as "DNA170021-2923".

Figure 368 shows the amino acid sequence (SEQ ID NO:368) derived from the coding sequence of SEQ ID NO:367 shown in Figure 367.

Figure 369 shows a nucleotide sequence (SEQ ID NO:369) of a native sequence PRO28631 cDNA, wherein SEQ ID NO:369 is a clone designated herein as "DNA170212-3000".

Figure 370 shows the amino acid sequence (SEQ ID NO:370) derived from the coding sequence of SEQ ID NO:369 shown in Figure 369.

Figure 371 shows a nucleotide sequence (SEQ ID NO:371) of a native sequence PRO21384 cDNA, wherein SEQ ID NO:371 is a clone designated herein as "DNA177313-2982".

Figure 372 shows the amino acid sequence (SEQ ID NO:372) derived from the coding sequence of SEQ ID NO:371 shown in Figure 371.

Figure 373 shows a nucleotide sequence (SEQ ID NO:373) of a native sequence PRO1449 cDNA, wherein SEQ ID NO:373 is a clone designated herein as "DNA64908-1163-1".

Figure 374 shows the amino acid sequence (SEQ ID NO:374) derived from the coding sequence of SEQ ID NO:373 shown in Figure 373.

Figure 375 shows wholemount in situ hybridization results on mouse embryos using a mouse orthologue of PRO1449 which has about 78% amino acid identity with PRO1449. The results show that PRO1449 orthologue is expressed in the developing vasculature. The cross-section further shows expression in endothelial cells and progenitors of endothelial cells.

Figure 376 shows that a PRO1449 orthologue having about 78% amino acid identity with PRO1449 is expressed in vasculature of many inflamed and diseased tissues, but is very low, or lacking, in normal adult vessels.

Figure 377 shows that a PRO1449 orthologue having about 78% amino acid identity with PRO1449 induces ectopic vessels in the eyes of chicken embryos.

5. Detailed Description of the Invention

5.1. Definitions

The phrases "cardiovascular, endothelial and angiogenic disorder", "cardiovascular, endothelial and angiogenic dysfunction", "cardiovascular, endothelial or angiogenic disorder" and "cardiovascular, endothelial or angiogenic dysfunction" are used interchangeably and refer in part to systemic disorders that affect vessels, such as diabetes mellitus, as well as diseases of the vessels themselves, such as of the arteries, capillaries, veins, and/or lymphatics. This would include indications that stimulate angiogenesis and/or cardiovascularization, and those that inhibit angiogenesis and/or cardiovascularization. Such disorders include, for example, arterial disease, such as atherosclerosis, hypertension, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; and other vascular disorders such as peripheral vascular disease, cancer such as vascular tumors, *e.g.*, hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma, tumor angiogenesis, trauma such as wounds, burns, and other injured tissue, implant fixation, scarring, ischemia reperfusion injury, rheumatoid arthritis, cerebrovascular disease, renal diseases such as acute renal failure, and osteoporosis. This would also include angina, myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as CHF.

"Hypertrophy", as used herein, is defined as an increase in mass of an organ or structure independent of natural growth that does not involve tumor formation. Hypertrophy of an organ or tissue is due either to an increase in the mass of the individual cells (true hypertrophy), or to an increase in the number of cells making up the tissue (hyperplasia), or both. Certain organs, such as the heart, lose the ability to divide shortly after birth. Accordingly, "cardiac hypertrophy" is defined as an increase in mass of the heart, which, in adults, is characterized by an increase in myocyte cell size and contractile protein content without concomitant cell division. The character of the stress responsible for inciting the hypertrophy, (*e.g.*, increased preload, increased afterload, loss of myocytes, as in myocardial infarction, or primary depression of contractility), appears to play a critical role in determining the nature of the response. The early stage of cardiac hypertrophy is usually characterized morphologically by increases in the size of myofibrils and mitochondria, as well as by enlargement of mitochondria and nuclei. At this stage, while muscle cells are larger than normal, cellular organization is largely preserved. At a more advanced stage of cardiac hypertrophy, there are preferential increases in the size or number of specific organelles, such as mitochondria, and new contractile elements are added in localized areas of the cells, in an irregular manner. Cells subjected to long-standing hypertrophy show more obvious disruptions in cellular organization, including markedly enlarged nuclei with highly lobulated membranes, which displace adjacent myofibrils and cause breakdown of normal Z-band registration. The phrase "cardiac hypertrophy" is used to include all stages of the progression of this condition, characterized by various degrees of structural damage of the heart muscle, regardless of the underlying cardiac disorder. Hence, the term also includes physiological conditions instrumental in the development of cardiac hypertrophy, such as elevated blood pressure, aortic stenosis, or myocardial infarction.

"Heart failure" refers to an abnormality of cardiac function where the heart does not pump blood at the rate

needed for the requirements of metabolizing tissues. The heart failure can be caused by a number of factors, including ischemic, congenital, rheumatic, or idiopathic forms.

"Congestive heart failure" (CHF) is a progressive pathologic state where the heart is increasingly unable to supply adequate cardiac output (the volume of blood pumped by the heart over time) to deliver the oxygenated blood to peripheral tissues. As CHF progresses, structural and hemodynamic damages occur. While these damages have a variety of manifestations, one characteristic symptom is ventricular hypertrophy. CHF is a common end result of a number of various cardiac disorders.

"Myocardial infarction" generally results from atherosclerosis of the coronary arteries, often with superimposed coronary thrombosis. It may be divided into two major types: transmural infarcts, in which myocardial necrosis involves the full thickness of the ventricular wall, and subendocardial (nontransmural) infarcts, in which the necrosis involves the subendocardium, the intramural myocardium, or both, without extending all the way through the ventricular wall to the epicardium. Myocardial infarction is known to cause both a change in hemodynamic effects and an alteration in structure in the damaged and healthy zones of the heart. Thus, for example, myocardial infarction reduces the maximum cardiac output and the stroke volume of the heart. Also associated with myocardial infarction is a stimulation of the DNA synthesis occurring in the interstice as well as an increase in the formation of collagen in the areas of the heart not affected.

As a result of the increased stress or strain placed on the heart in prolonged hypertension due, for example, to the increased total peripheral resistance, cardiac hypertrophy has long been associated with "hypertension". A characteristic of the ventricle that becomes hypertrophic as a result of chronic pressure overload is an impaired diastolic performance. Fouad *et al.*, J. Am. Coll. Cardiol., 4: 1500-1506 (1984); Smith *et al.*, J. Am. Coll. Cardiol., 5: 869-874 (1985). A prolonged left ventricular relaxation has been detected in early essential hypertension, in spite of normal or supranormal systolic function. Hartford *et al.*, Hypertension, 6: 329-338 (1984). However, there is no close parallelism between blood pressure levels and cardiac hypertrophy. Although improvement in left ventricular function in response to antihypertensive therapy has been reported in humans, patients variously treated with a diuretic (hydrochlorothiazide), a β-blocker (propranolol), or a calcium channel blocker (diltiazem), have shown reversal of left ventricular hypertrophy, without improvement in diastolic function. Inouye *et al.*, Am. J. Cardiol., 53: 1583-7 (1984).

Another complex cardiac disease associated with cardiac hypertrophy is "hypertrophic cardiomyopathy". This condition is characterized by a great diversity of morphologic, functional, and clinical features (Maron *et al.*, N. Engl. J. Med., 316: 780-789 (1987); Spirito *et al.*, N. Engl. J. Med., 320: 749-755 (1989); Louie and Edwards, Prog. Cardiovasc. Dis., 36: 275-308 (1994); Wigle *et al.*, Circulation, 92: 1680-1692 (1995)), the heterogeneity of which is accentuated by the fact that it afflicts patients of all ages. Spirito *et al.*, N. Engl. J. Med., 336: 775-785 (1997). The causative factors of hypertrophic cardiomyopathy are also diverse and little understood. In general, mutations in genes encoding sarcomeric proteins are associated with hypertrophic cardiomyopathy. Recent data suggest that β-myosin heavy chain mutations may account for approximately 30 to 40 percent of cases of familial hypertrophic cardiomyopathy. Watkins *et al.*, N. Engl. J. Med., 326: 1108-1114 (1992); Schwartz *et al*, Circulation, 91: 532-540 (1995); Marian and Roberts, Circulation, 92: 1336-1347 (1995); Thierfelder *et al.*, Cell, 77: 701-712

(1994); Watkins *et al.*, Nat. Gen., 11: 434-437 (1995). Besides β-myosin heavy chain, other locations of genetic mutations include cardiac troponin T, alpha topomyosin, cardiac myosin binding protein C, essential myosin light chain, and regulatory myosin light chain. *See*, Malik and Watkins, Curr. Opin. Cardiol., 12: 295-302 (1997).

Supravalvular "aortic stenosis" is an inherited vascular disorder characterized by narrowing of the ascending aorta, but other arteries, including the pulmonary arteries, may also be affected. Untreated aortic stenosis may lead to increased intracardiac pressure resulting in myocardial hypertrophy and eventually heart failure and death. The pathogenesis of this disorder is not fully understood, but hypertrophy and possibly hyperplasia of medial smooth muscle are prominent features of this disorder. It has been reported that molecular variants of the elastin gene are involved in the development and pathogenesis of aortic stenosis. U.S. Patent No. 5,650,282 issued July 22, 1997.

"Valvular regurgitation" occurs as a result of heart diseases resulting in disorders of the cardiac valves. Various diseases, like rheumatic fever, can cause the shrinking or pulling apart of the valve orifice, while other diseases may result in endocarditis, an inflammation of the endocardium or lining membrane of the atrioventricular orifices and operation of the heart. Defects such as the narrowing of the valve stenosis or the defective closing of the valve result in an accumulation of blood in the heart cavity or regurgitation of blood past the valve. If uncorrected, prolonged valvular stenosis or insufficiency may result in cardiac hypertrophy and associated damage to the heart muscle, which may eventually necessitate valve replacement.

The treatment of all these, and other cardiovascular, endothelial and angiogenic disorders, which may or may not be accompanied by cardiac hypertrophy, is encompassed by the present invention.

The terms "cancer", "cancerous", and "malignant" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include but are not limited to, carcinoma including adenocarcinoma, lymphoma, blastoma, melanoma, sarcoma, and leukemia. More particular examples of such cancers include squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, Hodgkin's and non-Hodgkin's lymphoma, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer such as hepatic carcinoma and hepatoma, bladder cancer, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, salivary gland carcinoma, kidney cancer such as renal cell carcinoma and Wilms' tumors, basal cell carcinoma, melanoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, esophageal cancer, and various types of head and neck cancer. The preferred cancers for treatment herein are breast, colon, lung, melanoma, ovarian, and others involving vascular tumors as noted above.

The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (*e.g.*, ^{131}I, ^{125}I, ^{90}Y, and ^{186}Re), chemotherapeutic agents, and toxins such as enzymatically active toxins of bacterial, fungal, plant, or animal origin, or fragments thereof.

A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer. Examples of chemotherapeutic agents include alkylating agents, folic acid antagonists, anti-metabolites of nucleic acid metabolism, antibiotics, pyrimidine analogs, 5-fluorouracil, cisplatin, purine nucleosides, amines, amino acids, triazol nucleosides, or corticosteroids. Specific examples include Adriamycin, Doxorubicin, 5-Fluorouracil,

Cytosine arabinoside ("Ara-C"), Cyclophosphamide, Thiotepa, Busulfan, Cytoxin, Taxol, Toxotere, Methotrexate, Cisplatin, Melphalan, Vinblastine, Bleomycin, Etoposide, Ifosfamide, Mitomycin C, Mitoxantrone, Vincreistine, Vinorelbine, Carboplatin, Teniposide, Daunomycin, Carminomycin, Aminopterin, Dactinomycin, Mitomycins, Esperamicins (*see* U.S. Pat. No. 4,675,187), Melphalan, and other related nitrogen mustards. Also included in this definition are hormonal agents that act to regulate or inhibit hormone action on tumors, such as tamoxifen and onapristone.

A "growth-inhibitory agent" when used herein refers to a compound or composition that inhibits growth of a cell, such as an Wnt-overexpressing cancer cell, either *in vitro* or *in vivo*. Thus, the growth-inhibitory agent is one which significantly reduces the percentage of malignant cells in S phase. Examples of growth-inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxol, and topo II inhibitors such as doxorubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in <u>The Molecular Basis of Cancer</u>, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogenes, and antineoplastic drugs" by Murakami *et al.* (WB Saunders: Philadelphia, 1995), especially p. 13. Additional examples include tumor necrosis factor (TNF), an antibody capable of inhibiting or neutralizing the angiogenic activity of acidic or basic FGF or hepatocyte growth factor (HGF), an antibody capable of inhibiting or neutralizing the coagulant activities of tissue factor, protein C, or protein S (*see*, WO 91/01753, published 21 February 1991), or an antibody capable of binding to HER2 receptor (WO 89/06692), such as the 4D5 antibody (and functional equivalents thereof) (*e.g.*, WO 92/22653).

"Treatment" is an intervention performed with the intention of preventing the development or altering the pathology of a cardiovascular, endothelial, and angiogenic disorder. The concept of treatment is used in the broadest sense, and specifically includes the prevention (prophylaxis), moderation, reduction, and curing of cardiovascular, endothelial, and angiogenic disorders of any stage. Accordingly, "treatment" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) or ameliorate a cardiovascular, endothelial, and angiogenic disorder such as hypertrophy. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented. The disorder may result from any cause, including idiopathic, cardiotrophic, or myotrophic causes, or ischemia or ischemic insults, such as myocardial infarction.

"Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to an acute mode, so as to maintain the initial effect, such as an anti-hypertrophic effect, for an extended period of time.

"Mammal" for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, sheep, pigs, etc. Preferably, the mammal is human.

Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

The phrase "cardiovascular, endothelial or angiogenic agents" refers generically to any drug that acts in treating cardiovascular, endothelial, and angiogenic disorders. Examples of cardiovascular agents are those that promote vascular homeostasis by modulating blood pressure, heart rate, heart contractility, and endothelial and smooth muscle biology, all of which factors have a role in cardiovascular disease. Specific examples of these include angiotensin-II receptor antagonists; endothelin receptor antagonists such as, for example, BOSENTAN™ and MOXONODIN™; interferon-gamma (IFN-γ); des-aspartate-angiotensin I; thrombolytic agents, *e.g.*, streptokinase, urokinase, t-PA, and a t-PA variant specifically designed to have longer half-life and very high fibrin specificity, TNK t-PA (a T103N, N117Q, KHRR(296-299)AAAA t-PA variant, Keyt *et al.*, Proc. Natl. Acad. Sci. USA, 91: 3670-3674 (1994)); inotropic or hypertensive agents such as digoxigenin and β-adrenergic receptor blocking agents, *e.g.*, propranolol, timolol, tertalolol, carteolol, nadolol, betaxolol, penbutolol, acetobutolol, atenolol, metoprolol, and carvedilol; angiotensin converting enzyme (ACE) inhibitors, *e.g.*, quinapril, captopril, enalapril, ramipril, benazepril, fosinopril, and lisinopril; diuretics, *e.g.*, chlorothiazide, hydrochlorothiazide, hydroflumethazide, methylchlothiazide, benzthiazide, dichlorphenamide, acetazolamide, and indapamide; and calcium channel blockers, *e.g.*, diltiazem, nifedipine, verapamil, nicardipine. One preferred category of this type is a therapeutic agent used for the treatment of cardiac hypertrophy or of a physiological condition instrumental in the development of cardiac hypertrophy, such as elevated blood pressure, aortic stenosis, or myocardial infarction.

"Angiogenic agents" and "endothelial agents" are active agents that promote angiogenesis and/or endothelial cell growth, or, if applicable, vasculogenesis. This would include factors that accelerate wound healing, such as growth hormone, insulin-like growth factor-I (IGF-I), VEGF, VIGF, PDGF, epidermal growth factor (EGF), CTGF and members of its family, FGF, and TGF-α and TGF-β.

"Angiostatic agents" are active agents that inhibit angiogenesis or vasculogenesis or otherwise inhibit or prevent growth of cancer cells. Examples include antibodies or other antagonists to angiogenic agents as defined above, such as antibodies to VEGF. They additionally include cytotherapeutic agents such as cytotoxic agents, chemotherapeutic agents, growth-inhibitory agents, apoptotic agents, and other agents to treat cancer, such as anti-HER-2, anti-CD20, and other bioactive and organic chemical agents.

In a pharmacological sense, in the context of the present invention, a "therapeutically effective amount" of an active agent such as a PRO polypeptide or agonist or antagonist thereto or an anti-PRO antibody, refers to an amount effective in the treatment of a cardiovascular, endothelial or angiogenic disorder in a mammal and can be determined empirically.

As used herein, an "effective amount" of an active agent such as a PRO polypeptide or agonist or antagonist thereto or an anti-PRO antibody, refers to an amount effective for carrying out a stated purpose, wherein such amounts may be determined empirically for the desired effect.

The terms "PRO polypeptide" and "PRO" as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (*i.e.*, PRO/number) refers to specific polypeptide sequences as described herein. The terms "PRO/number polypeptide" and "PRO/number" wherein the term "number" is provided as an actual numerical designation as used herein encompass native sequence polypeptides and polypeptide variants (which are further defined herein). The PRO polypeptides described herein

may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods.

A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO polypeptide (*e.g.*, an extracellular domain sequence), naturally-occurring variant forms (*e.g.*, alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence PRO polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons are shown in bold font and underlined in the figures. However, while the PRO polypeptide disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides.

The PRO polypeptide "extracellular domain" or "ECD" refers to a form of the PRO polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a PRO polypeptide ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the PRO polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein. Optionally, therefore, an extracellular domain of a PRO polypeptide may contain from about 5 or fewer amino acids on either side of the transmembrane domain/extracellular domain boundary as identified in the Examples or specification and such polypeptides, with or without the associated signal peptide, and nucleic acid encoding them, are contemplated by the present invention.

The approximate location of the "signal peptides" of the various PRO polypeptides disclosed herein are shown in the present specification and/or the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (*e.g.*, Nielsen *et al.*, Prot. Eng., 10:1-6 (1997) and von Heinje *et al.*, Nucl. Acids Res., 14:4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

"PRO polypeptide variant" means an active PRO polypeptide as defined above or below having at least about 80% amino acid sequence identity with a full-length native sequence PRO polypeptide sequence as disclosed

herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Such PRO polypeptide variants include, for instance, PRO polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a PRO polypeptide variant will have at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, PRO variant polypeptides are at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150 or 200 amino acids in length and alternatively at least about 300 amino acids in length, or more.

"Percent (%) amino acid sequence identity" with respect to the PRO polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in a PRO sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, ALIGN-2 or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full-length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are obtained as described below by using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code shown in Table 1 has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

For purposes herein, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction X/Y

where X is the number of amino acid residues scored as identical matches by the sequence alignment program

ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations, Tables 2-3 demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated "Comparison Protein" to the amino acid sequence designated "PRO".

Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described above using the ALIGN-2 sequence comparison computer program. However, % amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul *et al.*, Nucleic Acids Res., 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from http://www.ncbi.nlm.nih.gov. or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction X/Y

where X is the number of amino acid residues scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A.

In addition, % amino acid sequence identity may also be determined using the WU-BLAST-2 computer program (Altschul *et al.*, Methods in Enzymology, 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, *i.e.*, the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. For purposes herein, a % amino acid sequence identity value is determined by dividing (a) the number of matching identical amino acids residues between the amino acid sequence of the PRO polypeptide of interest having a sequence derived from the native PRO polypeptide and the comparison amino acid sequence of interest (*i.e.*, the sequence against which the PRO polypeptide of interest is being compared which may be a PRO variant polypeptide) as determined by WU-BLAST-2 by (b) the total number of amino acid residues of the PRO polypeptide of interest. For example, in the statement "a polypeptide comprising an amino acid sequence A which

has or having at least 80% amino acid sequence identity to the amino acid sequence B", the amino acid sequence A is the comparison amino acid sequence of interest and the amino acid sequence B is the amino acid sequence of the PRO polypeptide of interest.

"PRO variant polynucleotide" or "PRO variant nucleic acid sequence" means a nucleic acid molecule which encodes an active PRO polypeptide as defined below and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, a PRO variant polynucleotide will have at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% or 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity with a nucleic acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal sequence, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

Ordinarily, PRO variant polynucleotides are at least about 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 450, or 600 nucleotides in length and alternatively at least about 900 nucleotides in length, or more.

"Percent (%) nucleic acid sequence identity" with respect to the PRO polypeptide-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in a PRO polypeptide-encoding nucleic acid sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, ALIGN-2 or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full-length of the sequences being compared. For purposes herein, however, % nucleic acid sequence identity values are obtained as described below by using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code shown in Table 1 has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

For purposes herein, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that

has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

100 times the fraction W/Z

where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C. As examples of % nucleic acid sequence identity calculations, Tables 4-5 demonstrate how to calculate the % nucleic acid sequence identity of the nucleic acid sequence designated "Comparison DNA" to the nucleic acid sequence designated "PRO-DNA".

Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described above using the ALIGN-2 sequence comparison computer program. However, % nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul *et al.*, Nucleic Acids Res., 25:3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from http://www.ncbi.nlm.nih.gov. or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

100 times the fraction W/Z

where W is the number of nucleotides scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C.

In addition, % nucleic acid sequence identity values may also be generated using the WU-BLAST-2 computer program (Altschul *et al.*, Methods in Enzymology, 266:460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, *i.e.*, the adjustable parameters, are set with the following values: overlap span = 1, overlap fraction = 0.125, word threshold (T) = 11, and scoring matrix = BLOSUM62. For purposes herein, a % nucleic acid sequence identity value is determined by dividing (a)

the number of matching identical nucleotides between the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest having a sequence derived from the native sequence PRO polypeptide-encoding nucleic acid and the comparison nucleic acid molecule of interest (*i.e.*, the sequence against which the PRO polypeptide-encoding nucleic acid molecule of interest is being compared which may be a variant PRO polynucleotide) as determined by WU-BLAST-2 by (b) the total number of nucleotides of the PRO polypeptide-encoding nucleic acid molecule of interest. For example, in the statement "an isolated nucleic acid molecule comprising a nucleic acid sequence A which has or having at least 80% nucleic acid sequence identity to the nucleic acid sequence B", the nucleic acid sequence A is the comparison nucleic acid molecule of interest and the nucleic acid sequence B is the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest.

In other embodiments, PRO variant polynucleotides are nucleic acid molecules that encode an active PRO polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding the full-length PRO polypeptide as shown in the specification herein and accompanying figures. PRO variant polypeptides may be those that are encoded by a PRO variant polynucleotide.

"Isolated", when used to describe the various polypeptides disclosed herein, means a polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Preferably, the isolated polypeptide is free of association with all components with which it is naturally associated. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of the PRO natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

An "isolated" nucleic acid molecule encoding a PRO polypeptide or an "isolated" nucleic acid molecule encoding an anti-PRO antibody is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the PRO-encoding nucleic acid or the natural source of the anti-PRO-encoding nucleic acid. Preferably, the isolated nucleic acid is free of association with all components with which it is naturally associated. An isolated PRO-encoding nucleic acid molecule or an isolated anti-PRO-encoding nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated nucleic acid molecules therefore are distinguished from the PRO-encoding nucleic acid molecule or from the anti-PRO-encoding nucleic acid molecule as it exists in natural cells. However, an isolated nucleic acid molecule encoding a PRO polypeptide or an isolated nucleic acid molecule encoding an anti-PRO antibody includes PRO-nucleic acid molecules or anti-PRO-nucleic acid molecules contained in cells that ordinarily express PRO polypeptides or anti-PRO antibodies where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked

coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize, for example, promoters, polyadenylation signals, and enhancers.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a PRO polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in the same reading frame. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature that can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, *see*, Ausubel *et al.*, Current Protocols in Molecular Biology (Wiley Interscience Publishers, 1995).

"Stringent conditions" or "high-stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example, 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 μg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately-stringent conditions" may be identified as described by Sambrook *et al.*, Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Press, 1989), and include the use of washing solution and hybridization conditions (*e.g.*, temperature, ionic strength, and % SDS) less stringent than those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters

in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

The modifier "epitope-tagged" when used herein refers to a chimeric polypeptide comprising a PRO polypeptide fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

"Active" or "activity" in the context of PRO variants refers to form(s) of PRO proteins that retain the biologic and/or immunologic activities of a native or naturally-occurring PRO polypeptide.

"Biological activity" in the context of a molecule that antagonizes a PRO polypeptide that can be identified by the screening assays disclosed herein (*e.g.*, an organic or inorganic small molecule, peptide, etc.) is used to refer to the ability of such molecules to bind or complex with the PRO polypeptide identified herein, or otherwise interfere with the interaction of the PRO polypeptide with other cellular proteins or otherwise inhibits the transcription or translation of the PRO polypeptide. Particularly preferred biological activity includes cardiac hypertrophy, activity that acts on systemic disorders that affect vessels, such as diabetes mellitus, as well as diseases of the arteries, capillaries, veins, and/or lymphatics, and cancer.

The term "antagonist" is used in the broadest sense, and includes any molecule that partially or fully blocks, inhibits, or neutralizes one or more of the biological activities of a native PRO polypeptide disclosed herein, for example, if applicable, its mitogenic or angiogenic activity. Antagonists of a PRO polypeptide may act by interfering with the binding of a PRO polypeptide to a cellular receptor, by incapacitating or killing cells that have been activated by a PRO polypeptide, or by interfering with vascular endothelial cell activation after binding of a PRO polypeptide to a cellular receptor. All such points of intervention by a PRO polypeptide antagonist shall be considered equivalent for purposes of this invention. The antagonists inhibit the mitogenic, angiogenic, or other biological activity of PRO polypeptides, and thus are useful for the treatment of diseases or disorders characterized by undesirable excessive neovascularization, including by way of example tumors, and especially solid malignant tumors, rheumatoid arthritis, psoriasis, atherosclerosis, diabetic and other retinopathies, retrolental fibroplasia, age-related macular degeneration, neovascular glaucoma, hemangiomas, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, and chronic inflammation. The antagonists also are useful for the treatment of diseases or disorders characterized by undesirable excessive vascular permeability, such as edema associated with brain tumors, ascites associated with malignancies, Meigs' syndrome, lung inflammation, nephrotic syndrome, pericardial effusion (such as that associated with pericarditis), and pleural effusion. In a similar manner, the term "agonist" is used in the broadest sense and includes any molecule that mimics a biological activity of a native PRO polypeptide disclosed herein. Suitable agonist or antagonist molecules specifically include agonist or antagonist antibodies or antibody fragments, fragments, or amino acid sequence variants of native PRO polypeptides, peptides, small organic molecules, etc.

A "small molecule" is defined herein to have a molecular weight below about 500 daltons.

The term "PRO polypeptide receptor" as used herein refers to a cellular receptor for a PRO polypeptide, ordinarily a cell-surface receptor found on vascular endothelial cells, as well as variants thereof that retain the ability to bind a PRO polypeptide.

"Antibodies" (Abs) and "immunoglobulins" (Igs) are glycoproteins having the same structural characteristics. While antibodies exhibit binding specificity to a specific antigen, immunoglobulins include both antibodies and other antibody-like molecules that lack antigen specificity. Polypeptides of the latter kind are, for example, produced at low levels by the lymph system and at increased levels by myelomas. The term "antibody" is used in the broadest sense and specifically covers, without limitation, intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies) formed from at least two intact antibodies, and antibody fragments, so long as they exhibit the desired biological activity.

"Native antibodies" and "native immunoglobulins" are usually heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain at one end (V_L) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light-chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light- and heavy-chain variable domains.

The term "variable" refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody to and for its particular antigen. However, the variability is not evenly distributed throughout the variable domains of antibodies. It is concentrated in three segments called complementarity-determining regions (CDRs) or hypervariable regions both in the light-chain and the heavy-chain variable domains. The more highly conserved portions of variable domains are called the framework regions (FR). The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a β-sheet configuration, connected by three CDRs, which form loops connecting, and in some cases forming part of, the β-sheet structure. The CDRs in each chain are held together in close proximity by the FR regions and, with the CDRs from the other chain, contribute to the formation of the antigen-binding site of antibodies. *See*, Kabat *et al.*, NIH Publ. No.91-3242, Vol. I, pages 647-669 (1991). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody-dependent cellular toxicity.

"Antibody fragments" comprise a portion of an intact antibody, preferably the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies (Zapata *et al.*, Protein Eng., 8(10): 1057-1062 (1995)); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize

readily. Pepsin treatment yields an $F(ab')_2$ fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv" is the minimum antibody fragment that contains a complete antigen-recognition and -binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments that have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM; and several of these may be further divided into subclasses (isotypes), *e.g.*, IgG1, IgG2, IgG3, IgG4, IgA, and IgA2. The heavy-chain constant domains that correspond to the different classes of immunoglobulins are called α, δ, ϵ, γ, and μ, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler *et al.*, Nature, 256: 495 (1975), or may be made by recombinant DNA methods (*see, e.g.*, U.S. Patent No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson *et al.*, Nature, 352: 624-628 (1991) and Marks *et al.*, J. Mol. Biol., 222: 581-597 (1991), for example.

The monoclonal antibodies herein specifically include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity. U.S. Patent No. 4,816,567; Morrison *et al.*, Proc. Natl. Acad. Sci. USA, 81: 6851-6855 (1984).

"Humanized" forms of non-human (*e.g.*, murine) antibodies are chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequences of antibodies) that contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a CDR of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv FR residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences. These modifications are made to further refine and maximize antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin sequence. The humanized antibody preferably also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, *see* Jones *et al.*, Nature, 321: 522-525 (1986); Reichmann *et al.*, Nature, 332: 323-329 (1988); and Presta, Curr. Op. Struct. Biol., 2: 593-596 (1992). The humanized antibody includes a PRIMATIZED™ antibody wherein the antigen-binding region of the antibody is derived from an antibody produced by immunizing macaque monkeys with the antigen of interest.

"Single-chain Fv" or "sFv" antibody fragments comprise the V_H and V_L domains of an antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains that enables the sFv to form the desired structure for antigen binding. For a review of sFv *see*, Pluckthun in The Pharmacology of Monoclonal Antibodies, Vol. 113, Rosenburg and Moore, eds. (Springer-Verlag: New York, 1994), pp. 269-315.

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) in the same polypeptide chain (V_H - V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger *et al.*, Proc. Natl. Acad. Sci. USA, 90: 6444-6448 (1993).

An "isolated" antibody is one that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would interfere

with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant cells, since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

The word "label" when used herein refers to a detectable compound or other composition that is conjugated directly or indirectly to the antibody so as to generate a "labeled" antibody. The label may be detectable by itself (*e.g.*, radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition that is detectable. Radionuclides that can serve as detectable labels include, for example, I-131, I-123, I-125, Y-90, Re-188, At-211, Cu-67, Bi-212, and Pd-109. The label may also be a non-detectable entity such as a toxin.

By "solid phase" is meant a non-aqueous matrix to which an antibody of the present invention can adhere. Examples of solid phases encompassed herein include those formed partially or entirely of glass (*e.g.*, controlled pore glass), polysaccharides (*e.g.*, agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (*e.g.*, an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No. 4,275,149.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant that is useful for delivery of a drug (such as the PRO polypeptide or antibodies thereto disclosed herein) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

As used herein, the term "immunoadhesin" designates antibody-like molecules that combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity that is other than the antigen recognition and binding site of an antibody (*i.e.*, is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD, or IgM.

As shown below, Table 1 provides the complete source code for the ALIGN-2 sequence comparison computer program. This source code may be routinely compiled for use on a UNIX operating system to provide

the ALIGN-2 sequence comparison computer program.

In addition, Tables 2-5 show hypothetical exemplifications for using the below described method to determine % amino acid sequence identity (Tables 2-3) and % nucleic acid sequence identity (Tables 4-5) using the ALIGN-2 sequence comparison computer program, wherein "PRO" represents the amino acid sequence of a hypothetical PRO polypeptide of interest, "Comparison Protein" represents the amino acid sequence of a polypeptide against which the "PRO" polypeptide of interest is being compared, "PRO-DNA" represents a hypothetical PRO-encoding nucleic acid sequence of interest, "Comparison DNA" represents the nucleotide sequence of a nucleic acid molecule against which the "PRO-DNA" nucleic acid molecule of interest is being compared, "X", "Y", and "Z" each represent different hypothetical amino acid residues and "N", "L" and "V" each represent different hypothetical nucleotides.

Table 1

```
/*
 *
 * C-C increased from 12 to 15
 * Z is average of EQ
 * B is average of ND
 * match with stop is _M; stop-stop = 0; J (joker) match = 0
 */
#define  _M      -8        /* value of a match with a stop */

int      _day[26][26] = {
/*       A  B  C  D  E  F  G  H  I  J  K  L  M  N  O  P  Q  R  S  T  U  V  W  X  Y  Z */
/* A */  { 2, 0,-2, 0, 0,-4, 1,-1,-1, 0,-1,-2,-1, 0,_M, 1, 0,-2, 1, 1, 0, 0,-6, 0,-3, 0},
/* B */  { 0, 3,-4, 3, 2,-5, 0, 1,-2, 0, 0,-3,-2, 2,_M,-1, 1, 0, 0, 0, 0,-2,-5, 0,-3, 1},
/* C */  {-2,-4,15,-5,-5,-4,-3,-3,-2, 0,-5,-6,-5,-4,_M,-3,-5,-4, 0,-2, 0,-2,-8, 0, 0,-5},
/* D */  { 0, 3,-5, 4, 3,-6, 1, 1,-2, 0, 0,-4,-3, 2,_M,-1, 2,-1, 0, 0, 0,-2,-7, 0,-4, 2},
/* E */  { 0, 2,-5, 3, 4,-5, 0, 1,-2, 0, 0,-3,-2, 1,_M,-1, 2,-1, 0, 0, 0,-2,-7, 0,-4, 3},
/* F */  {-4,-5,-4,-6,-5, 9,-5,-2, 1, 0,-5, 2, 0,-4,_M,-5,-5,-4,-3,-3, 0,-1, 0, 0, 7,-5},
/* G */  { 1, 0,-3, 1, 0,-5, 5,-2,-3, 0,-2,-4,-3, 0,_M,-1,-1,-3, 1, 0, 0,-1,-7, 0,-5, 0},
/* H */  {-1, 1,-3, 1, 1,-2,-2, 6,-2, 0, 0,-2,-2, 2,_M, 0, 3, 2,-1,-1, 0,-2,-3, 0, 0, 2},
/* I */  {-1,-2,-2,-2,-2, 1,-3,-2, 5, 0,-2, 2, 2,-2,_M,-2,-2,-2,-1, 0, 0, 4,-5, 0,-1,-2},
/* J */  { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,_M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* K */  {-1, 0,-5, 0, 0,-5,-2, 0,-2, 0, 5,-3, 0, 1,_M,-1, 1, 3, 0, 0, 0,-2,-3, 0,-4, 0},
/* L */  {-2,-3,-6,-4,-3, 2,-4,-2, 2, 0,-3, 6, 4,-3,_M,-3,-2,-3,-3,-1, 0, 2,-2, 0,-1,-2},
/* M */  {-1,-2,-5,-3,-2, 0,-3,-2, 2, 0, 0, 4, 6,-2,_M,-2,-1, 0,-2,-1, 0, 2,-4, 0,-2,-1},
/* N */  { 0, 2,-4, 2, 1,-4, 0, 2,-2, 0, 1,-3,-2, 2,_M,-1, 1, 0, 1, 0, 0,-2,-4, 0,-2, 1},
/* O */  {_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M, 0,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M},
/* P */  { 1,-1,-3,-1,-1,-5,-1, 0,-2, 0,-1,-3,-2,-1,_M, 6, 0, 0, 1, 0, 0,-1,-6, 0,-5, 0},
/* Q */  { 0, 1,-5, 2, 2,-5,-1, 3,-2, 0, 1,-2,-1, 1,_M, 0, 4, 1,-1,-1, 0,-2,-5, 0,-4, 3},
/* R */  {-2, 0,-4,-1,-1,-4,-3, 2,-2, 0, 3,-3, 0, 0,_M, 0, 1, 6, 0,-1, 0,-2, 2, 0,-4, 0},
/* S */  { 1, 0, 0, 0, 0,-3, 1,-1,-1, 0, 0,-3,-2, 1,_M, 1,-1, 0, 2, 1, 0,-1,-2, 0,-3, 0},
/* T */  { 1, 0,-2, 0, 0,-3, 0,-1, 0, 0, 0,-1,-1, 0,_M, 0,-1,-1, 1, 3, 0, 0,-5, 0,-3, 0},
/* U */  { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,_M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* V */  { 0,-2,-2,-2,-2,-1,-1,-2, 4, 0,-2, 2, 2,-2,_M,-1,-2,-2,-1, 0, 0, 4,-6, 0,-2,-2},
/* W */  {-6,-5,-8,-7,-7, 0,-7,-3,-5, 0,-3,-2,-4,-4,_M,-6,-5, 2,-2,-5, 0,-6,17, 0, 0,-6},
/* X */  { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,_M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0},
/* Y */  {-3,-3, 0,-4,-4, 7,-5, 0,-1, 0,-4,-1,-2,-2,_M,-5,-4,-4,-3,-3, 0,-2, 0, 0,10,-4},
/* Z */  { 0, 1,-5, 2, 3,-5, 0, 2,-2, 0, 0,-2,-1, 1,_M, 0, 3, 0, 0, 0, 0,-2,-6, 0,-4, 4}
};
```

Table 1 (cont')

```
/*
 */
#include <stdio.h>
#include <ctype.h>

#define MAXJMP      16      /* max jumps in a diag */
#define MAXGAP      24      /* don't continue to penalize gaps larger than this */
#define JMPS        1024    /* max jmps in an path */
#define MX          4       /* save if there's at least MX-1 bases since last jmp */

#define DMAT        3       /* value of matching bases */
#define DMIS        0       /* penalty for mismatched bases */
#define DINS0       8       /* penalty for a gap */
#define DINS1       1       /* penalty per base */
#define PINS0       8       /* penalty for a gap */
#define PINS1       4       /* penalty per residue */

struct jmp {
        short           n[MAXJMP];      /* size of jmp (neg for dely) */
        unsigned short  x[MAXJMP];      /* base no. of jmp in seq x */
};                                      /* limits seq to 2^16 -1 */

struct diag {
        int             score;          /* score at last jmp */
        long            offset;         /* offset of prev block */
        short           ijmp;           /* current jmp index */
        struct jmp      jp;             /* list of jmps */
};

struct path {
        int     spc;            /* number of leading spaces */
        short   n[JMPS];        /* size of jmp (gap) */
        int     x[JMPS];        /* loc of jmp (last elem before gap) */
};

char            *ofile;                 /* output file name */
char            *namex[2];              /* seq names: getseqs( ) */
char            *prog;                  /* prog name for err msgs */
char            *seqx[2];                       /* seqs: getseqs( ) */
int             dmax;                   /* best diag: nw( ) */
int             dmax0;                  /* final diag */
int             dna;                    /* set if dna: main( ) */
int             endgaps;                /* set if penalizing end gaps */
int             gapx, gapy;             /* total gaps in seqs */
int             len0, len1;             /* seq lens */
int             ngapx, ngapy;           /* total size of gaps */
int             smax;                   /* max score: nw( ) */
int             *xbm;                   /* bitmap for matching */
long            offset;                 /* current offset in jmp file */
struct  diag    *dx;                    /* holds diagonals */
struct  path    pp[2];                  /* holds path for seqs */

char            *calloc( ), *malloc( ), *index( ), *strcpy( );
char            *getseq( ), *g_calloc( );
```

Table 1 (cont')

```
/* Needleman-Wunsch alignment program
 *
 * usage: progs file1 file2
 *   where file1 and file2 are two dna or two protein sequences.
 *   The sequences can be in upper- or lower-case an may contain ambiguity
 *   Any lines beginning with ';', '>' or '<' are ignored
 *   Max file length is 65535 (limited by unsigned short x in the jmp struct)
 *   A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
 *   Output is in the file "align.out"
 *
 * The program may create a tmp file in /tmp to hold info about traceback.
 * Original version developed under BSD 4.3 on a vax 8650
 */
#include "nw.h"
#include "day.h"

static   _dbval[26] = {
         1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
};

static   _pbval[26] = {
         1, 2|(1<<('D'-'A'))|(1<<('N'-'A')), 4, 8, 16, 32, 64,
         128, 256, 0xFFFFFFF, 1<<10, 1<<11, 1<<12, 1<<13, 1<<14,
         1<<15, 1<<16, 1<<17, 1<<18, 1<<19, 1<<20, 1<<21, 1<<22,
         1<<23, 1<<24, 1<<25|(1<<('E'-'A'))|(1<<('Q'-'A'))
};

main(ac, av)                                                                 main
         int     ac;
         char    *av[];
{
         prog = av[0];
         if (ac != 3) {
                  fprintf(stderr,"usage: %s file1 file2\n", prog);
                  fprintf(stderr,"where file1 and file2 are two dna or two protein sequences.\n");
                  fprintf(stderr,"The sequences can be in upper- or lower-case\n");
                  fprintf(stderr,"Any lines beginning with ';' or '<' are ignored\n");
                  fprintf(stderr,"Output is in the file \"align.out\"\n");
                  exit(1);
         }
         namex[0] = av[1];
         namex[1] = av[2];
         seqx[0] = getseq(namex[0], &len0);
         seqx[1] = getseq(namex[1], &len1);
         xbm = (dna)? _dbval : _pbval;

         endgaps = 0;                       /* 1 to penalize endgaps */
         ofile = "align.out";               /* output file */

         nw( );              /* fill in the matrix, get the possible jmps */
         readjmps( );        /* get the actual jmps */
         print( );           /* print stats, alignment */

         cleanup(0);         /* unlink any tmp files */
}
```

Table 1 (cont')

```
/* do the alignment, return best score: main( )
 * dna: values in Fitch and Smith, PNAS, 80, 1382-1386, 1983
 * pro: PAM 250 values
 * When scores are equal, we prefer mismatches to any gap, prefer
 * a new gap to extending an ongoing gap, and prefer a gap in seqx
 * to a gap in seq y.
 */
nw( )                                                                       nw
{
        char            *px, *py;               /* seqs and ptrs */
        int             *ndely, *dely;          /* keep track of dely */
        int             ndelx, delx;            /* keep track of delx */
        int             *tmp;                   /* for swapping row0, row1 */
        int             mis;                    /* score for each type */
        int             ins0, ins1;             /* insertion penalties */
        register        id;                     /* diagonal index */
        register        ij;                     /* jmp index */
        register        *col0, *col1;           /* score for curr, last row */
        register        xx, yy;                 /* index into seqs */

        dx = (struct diag *)g_calloc("to get diags", len0+len1+1, sizeof(struct diag));

        ndely = (int *)g_calloc("to get ndely", len1+1, sizeof(int));
        dely = (int *)g_calloc("to get dely", len1+1, sizeof(int));
        col0 = (int *)g_calloc("to get col0", len1+1, sizeof(int));
        col1 = (int *)g_calloc("to get col1", len1+1, sizeof(int));
        ins0 = (dna)? DINS0 : PINS0;
        ins1 = (dna)? DINS1 : PINS1;

        smax = -10000;
        if (endgaps) {
                for (col0[0] = dely[0] = -ins0, yy = 1; yy <= len1; yy++) {
                        col0[yy] = dely[yy] = col0[yy-1] - ins1;
                        ndely[yy] = yy;
                }
                col0[0] = 0;    /* Waterman Bull Math Biol 84 */
        }
        else
                for (yy = 1; yy <= len1; yy++)
                        dely[yy] = -ins0;

        /* fill in match matrix
         */
        for (px = seqx[0], xx = 1; xx <= len0; px++, xx++) {
                /* initialize first entry in col
                 */
                if (endgaps) {
                        if (xx == 1)
                                col1[0] = delx = -(ins0+ins1);
                        else
                                col1[0] = delx = col0[0] - ins1;
                        ndelx = xx;
                }
                else {
                        col1[0] = 0;
                        delx = -ins0;
                        ndelx = 0;
                }
```

Table 1 (cont')

...nw

```
for (py = seqx[1], yy = 1; yy <= len1; py++, yy++) {
        mis = col0[yy-1];
        if (dna)
                mis += (xbm[*px-'A']&xbm[*py-'A'])? DMAT : DMIS;
        else
                mis += _day[*px-'A'][*py-'A'];

        /* update penalty for del in x seq;
         * favor new del over ongong del
         * ignore MAXGAP if weighting endgaps
         */
        if (endgaps || ndely[yy] < MAXGAP) {
                if (col0[yy] - ins0 >= dely[yy]) {
                        dely[yy] = col0[yy] - (ins0+ins1);
                        ndely[yy] = 1;
                } else {
                        dely[yy] -= ins1;
                        ndely[yy]++;
                }
        } else {
                if (col0[yy] - (ins0+ins1) >= dely[yy]) {
                        dely[yy] = col0[yy] - (ins0+ins1);
                        ndely[yy] = 1;
                } else
                        ndely[yy]++;
        }

        /* update penalty for del in y seq;
         * favor new del over ongong del
         */
        if (endgaps || ndelx < MAXGAP) {
                if (col1[yy-1] - ins0 >= delx) {
                        delx = col1[yy-1] - (ins0+ins1);
                        ndelx = 1;
                } else {
                        delx -= ins1;
                        ndelx++;
                }
        } else {
                if (col1[yy-1] - (ins0+ins1) >= delx) {
                        delx = col1[yy-1] - (ins0+ins1);
                        ndelx = 1;
                } else
                        ndelx++;
        }

        /* pick the maximum score; we're favoring
         * mis over any del and delx over dely
         */
```

Table 1 (cont')

...nw

```
            id = xx - yy + len1 - 1;
            if (mis >= delx && mis >= dely[yy])
                    col1[yy] = mis;
            else if (delx >= dely[yy]) {
                    col1[yy] = delx;
                    ij = dx[id].ijmp;
                    if (dx[id].jp.n[0] && (!dna || (ndelx >= MAXJMP
                    && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
                            dx[id].ijmp++;
                            if (++ij >= MAXJMP) {
                                    writejmps(id);
                                    ij = dx[id].ijmp = 0;
                                    dx[id].offset = offset;
                                    offset += sizeof(struct jmp) + sizeof(offset);
                            }
                    }
                    dx[id].jp.n[ij] = ndelx;
                    dx[id].jp.x[ij] = xx;
                    dx[id].score = delx;
            }
            else {
                    col1[yy] = dely[yy];
                    ij = dx[id].ijmp;
if (dx[id].jp.n[0] && (!dna || (ndely[yy] >= MAXJMP
                    && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
                            dx[id].ijmp++;
                            if (++ij >= MAXJMP) {
                                    writejmps(id);
                                    ij = dx[id].ijmp = 0;
                                    dx[id].offset = offset;
                                    offset += sizeof(struct jmp) + sizeof(offset);
                            }
                    }
                    dx[id].jp.n[ij] = -ndely[yy];
                    dx[id].jp.x[ij] = xx;
                    dx[id].score = dely[yy];
            }
            if (xx == len0 && yy < len1) {
                    /* last col
                     */
                    if (endgaps)
                            col1[yy] -= ins0+ins1*(len1-yy);
                    if (col1[yy] > smax) {
                            smax = col1[yy];
                            dmax = id;
                    }
            }
    }
    if (endgaps && xx < len0)
            col1[yy-1] -= ins0+ins1*(len0-xx);
    if (col1[yy-1] > smax) {
            smax = col1[yy-1];
            dmax = id;
    }
    tmp = col0; col0 = col1; col1 = tmp;
}
(void) free((char *)ndely);
(void) free((char *)dely);
(void) free((char *)col0);
(void) free((char *)col1);                }
```

Table 1 (cont')

```
/*
 *
 * print( ) -- only routine visible outside this module
 *
 * static:
 * getmat( ) -- trace back best path, count matches: print( )
 * pr_align( ) -- print alignment of described in array p[]: print( )
 * dumpblock( ) -- dump a block of lines with numbers, stars: pr_align( )
 * nums( ) -- put out a number line: dumpblock( )
 * putline( ) -- put out a line (name, [num], seq, [num]): dumpblock( )
 * stars( ) - -put a line of stars: dumpblock( )
 * stripname( ) -- strip any path and prefix from a seqname
 */

#include "nw.h"

#define SPC       3
#define P_LINE    256       /* maximum output line */
#define P_SPC     3         /* space between name or num and seq */

extern    _day[26][26];
int       olen;             /* set output line length */
FILE      *fx;              /* output file */

print( )                                                              print
{
        int       lx, ly, firstgap, lastgap;      /* overlap */

        if ((fx = fopen(ofile, "w")) == 0) {
                fprintf(stderr,"%s: can't write %s\n", prog, ofile);
                cleanup(1);
        }
        fprintf(fx, "<first sequence: %s (length = %d)\n", namex[0], len0);
        fprintf(fx, "<second sequence: %s (length = %d)\n", namex[1], len1);
        olen = 60;
        lx = len0;
        ly = len1;
        firstgap = lastgap = 0;
        if (dmax < len1 - 1) {          /* leading gap in x */
                pp[0].spc = firstgap = len1 - dmax - 1;
                ly -= pp[0].spc;
        }
        else if (dmax > len1 - 1) {  /* leading gap in y */
                pp[1].spc = firstgap = dmax - (len1 - 1);
                lx -= pp[1].spc;
        }
        if (dmax0 < len0 - 1) {         /* trailing gap in x */
                lastgap = len0 - dmax0 -1;
                lx -= lastgap;
        }
        else if (dmax0 > len0 - 1) { /* trailing gap in y */
                lastgap = dmax0 - (len0 - 1);
                ly -= lastgap;
        }
        getmat(lx, ly, firstgap, lastgap);
        pr_align( );
}
```

Table 1 (cont')

getmat

```
/*
 * trace back the best path, count matches
 */
static
getmat(lx, ly, firstgap, lastgap)
	int	lx, ly;			/* "core" (minus endgaps) */
	int	firstgap, lastgap;	/* leading trailing overlap */
{
	int		nm, i0, i1, siz0, siz1;
	char		outx[32];
	double		pct;
	register	n0, n1;
	register char	*p0, *p1;

	/* get total matches, score
	 */
	i0 = i1 = siz0 = siz1 = 0;
	p0 = seqx[0] + pp[1].spc;
	p1 = seqx[1] + pp[0].spc;
	n0 = pp[1].spc + 1;
	n1 = pp[0].spc + 1;

	nm = 0;
	while ( *p0 && *p1 ) {
		if (siz0) {
			p1++;
			n1++;
			siz0--;
		}
		else if (siz1) {
			p0++;
			n0++;
			siz1--;
		}
		else {
			if (xbm[*p0-'A']&xbm[*p1-'A'])
				nm++;
			if (n0++ == pp[0].x[i0])
				siz0 = pp[0].n[i0++];
			if (n1++ == pp[1].x[i1])
				siz1 = pp[1].n[i1++];
			p0++;
			p1++;
		}
	}

	/* pct homology:
	 * if penalizing endgaps, base is the shorter seq
	 * else, knock off overhangs and take shorter core
	 */
	if (endgaps)
		lx = (len0 < len1)? len0 : len1;
	else
		lx = (lx < ly)? lx : ly;
	pct = 100.*(double)nm/(double)lx;
	fprintf(fx, "\n");
	fprintf(fx, "<%d match%s in an overlap of %d: %.2f percent similarity\n",
		nm, (nm == 1)? "" : "es", lx, pct);
```

Table 1 (cont')

...getmat

```
	fprintf(fx, "<gaps in first sequence: %d", gapx);
	if (gapx) {
		(void) sprintf(outx, " (%d %s%s)",
			ngapx, (dna)? "base":"residue", (ngapx == 1)? "":"s");
		fprintf(fx,"%s", outx);

	fprintf(fx, ", gaps in second sequence: %d", gapy);
	if (gapy) {
		(void) sprintf(outx, " (%d %s%s)",
			ngapy, (dna)? "base":"residue", (ngapy == 1)? "":"s");
		fprintf(fx,"%s", outx);
	}
	if (dna)
		fprintf(fx,
		"\n<score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per base)\n",
		smax, DMAT, DMIS, DINS0, DINS1);
	else
		fprintf(fx,
		"\n<score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
		smax, PINS0, PINS1);
	if (endgaps)
		fprintf(fx,
		"<endgaps penalized. left endgap: %d %s%s, right endgap: %d %s%s\n",
		firstgap, (dna)? "base" : "residue", (firstgap == 1)? "" : "s",
		lastgap, (dna)? "base" : "residue", (lastgap == 1)? "" : "s");
	else
		fprintf(fx, "<endgaps not penalized\n");
}

static		nm;		/* matches in core -- for checking */
static		lmax;		/* lengths of stripped file names */
static		ij[2];		/* jmp index for a path */
static		nc[2];		/* number at start of current line */
static		ni[2];		/* current elem number -- for gapping */
static		siz[2];
static char	*ps[2];		/* ptr to current element */
static char	*po[2];		/* ptr to next output char slot */
static char	out[2][P_LINE];	/* output line */
static char	star[P_LINE];	/* set by stars( ) */

/*
 * print alignment of described in struct path pp[]
 */
static
pr_align( )
{
	int		nn;	/* char count */
	int		more;
	register	i;

	for (i = 0, lmax = 0; i < 2; i++) {
		nn = stripname(namex[i]);
		if (nn > lmax)
			lmax = nn;

		nc[i] = 1;
		ni[i] = 1;
		siz[i] = ij[i] = 0;
		ps[i] = seqx[i];
		po[i] = out[i];			}
```

pr_align

Table 1 (cont')

...pr_align

```
	for (nn = nm = 0, more = 1; more; ) {
		for (i = more = 0; i < 2; i++) {
			/*
			 * do we have more of this sequence?
			 */
			if (!*ps[i])
				continue;

			more++;

			if (pp[i].spc) {	/* leading space */
				*po[i]++ = ' ';
				pp[i].spc--;
			}
			else if (siz[i]) {	/* in a gap */
				*po[i]++ = '-';
				siz[i]--;
			}
			else {			/* we're putting a seq element
						 */
				*po[i] = *ps[i];
				if (islower(*ps[i]))
					*ps[i] = toupper(*ps[i]);
				po[i]++;
				ps[i]++;

				/*
				 * are we at next gap for this seq?
				 */
				if (ni[i] == pp[i].x[ij[i]]) {
					/*
					 * we need to merge all gaps
					 * at this location
					 */
					siz[i] = pp[i].n[ij[i]++];
					while (ni[i] == pp[i].x[ij[i]])
						siz[i] += pp[i].n[ij[i]++];
				}
				ni[i]++;
			}
		}
		if (++nn == olen || !more && nn) {
			dumpblock( );
			for (i = 0; i < 2; i++)
				po[i] = out[i];
			nn = 0;
		}
	}
}

/*
 * dump a block of lines, including numbers, stars: pr_align( )
 */
static
dumpblock( )
{
	register	i;

	for (i = 0; i < 2; i++)
*po[i]-- = '\0';
```

dumpblock

Table 1 (cont')

...dumpblock

```
        (void) putc('\n', fx);
        for (i = 0; i < 2; i++) {
                if (*out[i] && (*out[i] != ' ' || *(po[i]) != ' ')) {
                        if (i == 0)
                                nums(i);
                        if (i == 0 && *out[1])
                                stars( );
                        putline(i);
                        if (i == 0 && *out[1])
                                fprintf(fx, star);
                        if (i == 1)
                                nums(i);
                }
        }
}

/*
 * put out a number line: dumpblock( )
 */
static
nums(ix)
        int     ix;     /* index in out[] holding seq line */
{
        char            nline[P_LINE];
        register        i, j;
        register char   *pn, *px, *py;

        for (pn = nline, i = 0; i < lmax+P_SPC; i++, pn++)
                *pn = ' ';
        for (i = nc[ix], py = out[ix]; *py; py++, pn++) {
                if (*py == ' ' || *py == '-')
                        *pn = ' ';
                else {
                        if (i%10 == 0 || (i == 1 && nc[ix] != 1)) {
                                j = (i < 0)? -i : i;
                                for (px = pn; j; j /= 10, px--)
                                        *px = j%10 + '0';
                                if (i < 0)
                                        *px = '-';
                        }
                        else
                                *pn = ' ';
                        i++;
                }
        }
        *pn = '\0';
        nc[ix] = i;
        for (pn = nline; *pn; pn++)
                (void) putc(*pn, fx);
        (void) putc('\n', fx);
}
```

nums

```
/*
 * put out a line (name, [num], seq, [num]): dumpblock( )
 */
static
putline(ix)
        int     ix;                     {
```

putline

Table 1 (cont')

...putline

```
        int             i;
        register char   *px;

        for (px = namex[ix], i = 0; *px && *px != ':'; px++, i++)
                (void) putc(*px, fx);
        for (; i < lmax+P_SPC; i++)
                (void) putc(' ', fx);

        /* these count from 1:
         * ni[] is current element (from 1)
         * nc[] is number at start of current line
         */
        for (px = out[ix]; *px; px++)
                (void) putc(*px&0x7F, fx);
        (void) putc('\n', fx);
}
```

```
/*
 * put a line of stars (seqs always in out[0], out[1]): dumpblock( )
 */
static
stars( )
{
        int             i;
        register char   *p0, *p1, cx, *px;

        if (!*out[0] || (*out[0] == ' ' && *(po[0]) == ' ') ||
           !*out[1] || (*out[1] == ' ' && *(po[1]) == ' '))
                return;
        px = star;
        for (i = lmax+P_SPC; i; i--)
                *px++ = ' ';

        for (p0 = out[0], p1 = out[1]; *p0 && *p1; p0++, p1++) {
                if (isalpha(*p0) && isalpha(*p1)) {

                        if (xbm[*p0-'A']&xbm[*p1-'A']) {
                                cx = '*';
                                nm++;
                        }
                        else if (!dna && _day[*p0-'A'][*p1-'A'] > 0)
                                cx = '.';
                        else
                                cx = ' ';
                }
                else
                        cx = ' ';
                *px++ = cx;
        }
        *px++ = '\n';
        *px = '\0';
}
```

stars

Table 1 (cont')

stripname

```
/*
 * strip path or prefix from pn, return len: pr_align( )
 */
static
stripname(pn)
        char    *pn;    /* file name (may be path) */
{
        register char    *px, *py;

        py = 0;
        for (px = pn; *px; px++)
                if (*px == '/')
                        py = px + 1;
        if (py)
                (void) strcpy(pn, py);
        return(strlen(pn));

}
```

Table 1 (cont')

```
/*
 * cleanup( ) -- cleanup any tmp file
 * getseq( ) -- read in seq, set dna, len, maxlen
 * g_calloc( ) -- calloc( ) with error checkin
 * readjmps( ) -- get the good jmps, from tmp file if necessary
 * writejmps( ) -- write a filled array of jmps to a tmp file: nw( )
 */
#include "nw.h"
#include <sys/file.h>

char    *jname = "/tmp/homgXXXXXX";          /* tmp file for jmps */
FILE    *fj;

int     cleanup( );                          /* cleanup tmp file */
long    lseek( );

/*
 * remove any tmp file if we blow
 */
cleanup(i)                                                          cleanup
        int     i;
{
        if (fj)
                (void) unlink(jname);
        exit(i);
}

/*
 * read, return ptr to seq, set dna, len, maxlen
 * skip lines starting with ';', '<', or '>'
 * seq in upper or lower case
 */
char    *
getseq(file, len)                                                   getseq
        char    *file;  /* file name */
        int     *len;   /* seq len */
{
        char            line[1024], *pseq;
        register char   *px, *py;
        int             natgc, tlen;
        FILE            *fp;

        if ((fp = fopen(file,"r")) == 0) {
                fprintf(stderr,"%s: can't read %s\n", prog, file);
                exit(1);
        }
        tlen = natgc = 0;
        while (fgets(line, 1024, fp)) {
                if (*line == ';' || *line == '<' || *line == '>')
                        continue;
                for (px = line; *px != '\n'; px++)
                        if (isupper(*px) || islower(*px))
                                tlen++;
        }
        if ((pseq = malloc((unsigned)(tlen+6))) == 0) {
                fprintf(stderr,"%s: malloc( ) failed to get %d bytes for %s\n", prog, tlen+6, file);
                exit(1);
        }
        pseq[0] = pseq[1] = pseq[2] = pseq[3] = '\0';
```

Table 1 (cont')

...getseq

```
	py = pseq + 4;
	*len = tlen;
	rewind(fp);

	while (fgets(line, 1024, fp)) {
		if (*line == ';' || *line == '<' || *line == '>')
			continue;
		for (px = line; *px != '\n'; px++) {
			if (isupper(*px))
				*py++ = *px;
			else if (islower(*px))
				*py++ = toupper(*px);
			if (index("ATGCU",*(py-1)))
				natgc++;
		}
	}
	*py++ = '\0';
	*py = '\0';
	(void) fclose(fp);
	dna = natgc > (tlen/3);
	return(pseq+4);
}

char	*
g_calloc(msg, nx, sz)
	char	*msg;		/* program, calling routine */
	int	nx, sz;		/* number and size of elements */
{
	char		*px, *calloc( );

	if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
		if (*msg) {
			fprintf(stderr, "%s: g_calloc( ) failed %s (n=%d, sz=%d)\n", prog, msg, nx, sz);
			exit(1);
		}
	}
	return(px);
}
```

g_calloc

```
/*
 * get final jmps from dx[] or tmp file, set pp[], reset dmax: main( )
 */
readjmps( )
{
	int		fd = -1;
	int		siz, i0, i1;
	register	i, j, xx;

	if (fj) {
		(void) fclose(fj);
		if ((fd = open(jname, O_RDONLY, 0)) < 0) {
			fprintf(stderr, "%s: can't open( ) %s\n", prog, jname);
			cleanup(1);
		}
	}
	for (i = i0 = i1 = 0, dmax0 = dmax, xx = len0; ; i++) {
		while (1) {
			for (j = dx[dmax].ijmp; j >= 0 && dx[dmax].jp.x[j] >= xx; j--)
				;
```

readjmps

Table 1 (cont')

...readjmps

```
                        if (j < 0 && dx[dmax].offset && fj) {
                                (void) lseek(fd, dx[dmax].offset, 0);
                                (void) read(fd, (char *)&dx[dmax].jp, sizeof(struct jmp));
                                (void) read(fd, (char *)&dx[dmax].offset, sizeof(dx[dmax].offset));
                                dx[dmax].ijmp = MAXJMP-1;
                        }
                        else
                                break;
                }
                if (i >= JMPS) {
                        fprintf(stderr, "%s: too many gaps in alignment\n", prog);
                        cleanup(1);
                }
                if (j >= 0) {
                        siz = dx[dmax].jp.n[j];
                        xx = dx[dmax].jp.x[j];
                        dmax += siz;
                        if (siz < 0) {          /* gap in second seq */
                                pp[1].n[i1] = -siz;
                                xx += siz;
                                /* id = xx - yy + len1 - 1
                                 */
                                pp[1].x[i1] = xx - dmax + len1 - 1;
                                gapy++;
                                ngapy -= siz;
/* ignore MAXGAP when doing endgaps */
                                siz = (-siz < MAXGAP || endgaps)? -siz : MAXGAP;
                                i1++;
                        }
                        else if (siz > 0) {  /* gap in first seq */
                                pp[0].n[i0] = siz;
                                pp[0].x[i0] = xx;
                                gapx++;
                                ngapx += siz;
/* ignore MAXGAP when doing endgaps */
                                siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
                                i0++;
                        }
                }
                else
                        break;
        }

        /* reverse the order of jmps
         */
        for (j = 0, i0--; j < i0; j++, i0--) {
                i = pp[0].n[j]; pp[0].n[j] = pp[0].n[i0]; pp[0].n[i0] = i;
                i = pp[0].x[j]; pp[0].x[j] = pp[0].x[i0]; pp[0].x[i0] = i;
        }
        for (j = 0, i1--; j < i1; j++, i1--) {
                i = pp[1].n[j]; pp[1].n[j] = pp[1].n[i1]; pp[1].n[i1] = i;
                i = pp[1].x[j]; pp[1].x[j] = pp[1].x[i1]; pp[1].x[i1] = i;
        }
        if (fd >= 0)
                (void) close(fd);
        if (fj) {
                (void) unlink(jname);
                fj = 0;
                offset = 0;     }                               }
```

Table 1 (cont')

writejmps

```
/*
 * write a filled jmp struct offset of the prev one (if any): nw( )
 */
writejmps(ix)
        int     ix;
{
        char    *mktemp( );

        if (!fj) {
                if (mktemp(jname) < 0) {
                        fprintf(stderr, "%s: can't mktemp( ) %s\n", prog, jname);
                        cleanup(1);
                }
                if ((fj = fopen(jname, "w")) == 0) {
                        fprintf(stderr, "%s: can't write %s\n", prog, jname);
                        exit(1);
                }
        }
        (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
        (void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
}
```

Table 2

PRO	XXXXXXXXXXXXXXX	(Length = 15 amino acids)
Comparison Protein	XXXXXYYYYYYY	(Length = 12 amino acids)

% amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =

5 divided by 15 = 33.3%

Table 3

PRO	XXXXXXXXXX	(Length = 10 amino acids)
Comparison Protein	XXXXXYYYYYYZZYZ	(Length = 15 amino acids)

% amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) =

5 divided by 10 = 50%

Table 4

PRO-DNA	NNNNNNNNNNNNNN	(Length = 14 nucleotides)
Comparison DNA	NNNNNNLLLLLLLLLL	(Length = 16 nucleotides)

% nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

6 divided by 14 = 42.9%

Table 5

PRO-DNA	NNNNNNNNNNNN	(Length = 12 nucleotides)
Comparison DNA	NNNNLLLVV	(Length = 9 nucleotides)

% nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) =

4 divided by 12 = 33.3%

5.2. Compositions and Methods of the Invention

5.2.1. PRO Variants

In addition to the full-length native sequence PRO polypeptides described herein, it is contemplated that PRO variants can be prepared. PRO variants can be prepared by introducing appropriate nucleotide changes into the PRO DNA, and/or by synthesis of the desired PRO polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of the PRO polypeptide such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

Variations in the native full-length sequence PRO polypeptide or in various domains of the PRO polypeptide described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a substitution, deletion or insertion of one or more codons encoding the PRO polypeptide that results in a change in the amino acid sequence of the PRO polypeptide as compared with the native sequence PRO polypetide. Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the PRO polypeptide. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the PRO polypeptide with that of homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, *i.e.*, conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 1 to 5 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

In particular embodiments, conservative substitutions of interest are shown in Table 6 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial changes, denominated exemplary substitutions in Table 6, or as further described below in reference to amino acid classes, are introduced and the products screened.

Table 6

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	val; leu; ile	val
Arg (R)	lys; gln; asn	lys
Asn (N)	gln; his; lys; arg	gln
Asp (D)	glu	glu
Cys (C)	ser	ser
Gln (Q)	asn	asn
Glu (E)	asp	asp
Gly (G)	pro; ala	ala
His (H)	asn; gln; lys; arg	arg
Ile (I)	leu; val; met; ala; phe; norleucine	leu
Leu (L)	norleucine; ile; val; met; ala; phe	ile
Lys (K)	arg; gln; asn	arg
Met (M)	leu; phe; ile	leu
Phe (F)	leu; val; ile; ala; tyr	leu
Pro (P)	ala	ala
Ser (S)	thr	thr
Thr (T)	ser	ser
Trp (W)	tyr; phe	tyr
Tyr (Y)	trp; phe; thr; ser	phe
Val (V)	ile; leu; met; phe; ala; norleucine	leu

Substantial modifications in function or immunological identity of the PRO polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

(1) hydrophobic: norleucine, met, ala, val, leu, ile;

(2) neutral hydrophilic: cys, ser, thr;

(3) acidic: asp, glu;

(4) basic: asn, gln, his, lys, arg;

(5) residues that influence chain orientation: gly, pro; and

(6) aromatic: trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter *et al.*, Nucl. Acids Res., 13:4331 (1986); Zoller *et al.*, Nucl. Acids Res., 10:6487 (1987)], cassette mutagenesis [Wells *et al.*, Gene, 34:315 (1985)], restriction selection mutagenesis [Wells *et al.*, Philos. Trans. R. Soc. London SerA, 317:415

(1986)] or other known techniques can be performed on the cloned DNA to produce the PRO variant DNA.

Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, Science, 244: 1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, The Proteins, (W.H. Freeman & Co., N.Y.); Chothia, J. Mol. Biol., 150:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

5.2.2. Modifications of PRO Polypeptides

Covalent modifications of PRO polypeptides are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of a PRO polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C- terminal residues of the PRO polypeptide. Derivatization with bifunctional agents is useful, for instance, for crosslinking the PRO polypeptide to a water-insoluble support matrix or surface for use in the method for purifying anti-PRO antibodies, and vice-versa. Commonly used crosslinking agents include, *e.g.*, 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimidate.

Other modifications include deamidation of glutaminyl and asparaginyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α-amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the PRO polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in the native sequence PRO polypeptide (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence PRO polypeptide. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Addition of glycosylation sites to the PRO polypeptide may be accomplished by altering the amino acid sequence. The alteration may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues to the native sequence PRO polypeptide (for O-linked glycosylation sites). The PRO amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the PRO polypeptide at preselected bases such that codons are generated that will translate into the desired amino

acids.

Another means of increasing the number of carbohydrate moieties on the PRO polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, *e.g.*, in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, CRC Crit. Rev. Biochem., pp. 259-306 (1981).

Removal of carbohydrate moieties present on the PRO polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, *et al.*, Arch. Biochem. Biophys., 259:52 (1987) and by Edge *et al.*, Anal. Biochem., 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura *et al.*, Meth. Enzymol., 138:350 (1987).

Another type of covalent modification of the PRO polypeptide comprises linking the PRO polypeptide to one of a variety of nonproteinaceous polymers, *e.g.*, polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337.

The PRO polypeptide of the present invention may also be modified in a way to form a chimeric molecule comprising the PRO polypeptide fused to another, heterologous polypeptide or amino acid sequence.

In one embodiment, such a chimeric molecule comprises a fusion of the PRO polypeptide with a protein transduction domain which targets the PRO polypeptide for delivery to various tissues and more particularly across the brain blood barrier, using, for example, the protein transduction domain of human immunodeficiency virus TAT protein (Schwarze *et al.*, 1999, Science 285: 1569-72).

In another embodiment, such a chimeric molecule comprises a fusion of the PRO polypeptide with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the PRO polypeptide. The presence of such epitope-tagged forms of the PRO polypeptide can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the PRO polypeptide to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-His) or poly-histidine-glycine (poly-His-gly) tags; the flu HA tag polypeptide and its antibody 12CA5 [Field *et al.*, Mol. Cell. Biol., 8:2159-2165 (1988)]; the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan *et al.*, Molecular and Cellular Biology, 5:3610-3616 (1985)]; and the Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky *et al.*, Protein Engineering, 3(6):547-553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp *et al.*, BioTechnology, 6:1204-1210 (1988)]; the KT3 epitope peptide [Martin *et al.*, Science, 255:192-194 (1992)]; an α-tubulin epitope peptide [Skinner *et al.*, J. Biol. Chem., 266:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-Freyermuth *et al.*, Proc. Natl. Acad. Sci. USA, 87:6393-6397 (1990)].

In an alternative embodiment, the chimeric molecule may comprise a fusion of the PRO polypeptide with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule (also referred to as an "immunoadhesin"), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions

preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of a PRO polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred embodiment, the immunoglobulin fusion includes the hinge, CH2 and CH3, or the hinge, CH1, CH2 and CH3 regions of an IgG1 molecule. For the production of immunoglobulin fusions *see* also, U.S. Patent No. 5,428,130 issued June 27, 1995.

5.2.3. Preparation of the PRO Polypeptide

The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO polypeptides. In particular, cDNAs encoding PRO polypeptides have been identified and isolated, as disclosed in further detail in the Examples below. It is noted that proteins produced in separate expression rounds may be given different PRO numbers but the UNQ number is unique for any given DNA and the encoded protein, and will not be changed. However, for sake of simplicity, in the present specification the protein encoded by the PRO DNA as well as all further native homologues and variants included in the foregoing definition of PRO polypeptides, will be referred to as "PRO" regardless of their origin or mode of preparation.

The description below relates primarily to production of PRO polypeptides by culturing cells transformed or transfected with a vector containing nucleic acid encoding PRO polypeptides. It is, of course, contemplated that alternative methods that are well known in the art may be employed to prepare the PRO polypeptide. For instance, the PRO polypeptide sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques. *See, e.g.*, Stewart *et al.*, Solid-Phase Peptide Synthesis (W.H. Freeman Co.: San Francisco, CA, 1969); Merrifield, J. Am. Chem. Soc., 85: 2149-2154 (1963). *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, with an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the PRO polypeptide may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the full-length PRO polypeptide.

5.2.3.1. Isolation of DNA Encoding PRO Polypeptides

DNA encoding the PRO polypeptide may be obtained from a cDNA library prepared from tissue believed to possess the mRNA encoding the PRO polypeptide and to express it at a detectable level. Accordingly, DNAs encoding the human PRO polypeptide can be conveniently obtained from cDNA libraries prepared from human tissues, such as described in the Examples. The gene encoding the PRO polypeptide may also be obtained from a genomic library or by oligonucleotide synthesis.

Libraries can be screened with probes (such as antibodies to the PRO polypeptide or oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook *et al.*, *supra*. An alternative means to isolate the gene encoding the PRO polypeptide is to use PCR methodology. Sambrook *et al.*, *supra*; Dieffenbach *et al.*, PCR Primer: A Laboratory Manual (New York: Cold

Spring Harbor Laboratory Press, 1995).

The Examples below describe techniques for screening a cDNA library. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like ^{32}P-labeled ATP, biotinylation, or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook *et al.*, *supra.*

Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined through sequence alignment using computer software programs such as ALIGN, DNAstar, and INHERIT, which employ various algorithms to measure homology.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook *et al.*, *supra,* to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

5.2.3.2. Selection and Transformation of Host Cells

Host cells are transfected or transformed with expression or cloning vectors described herein for PRO polypeptide production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH, and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: A Practical Approach, M. Butler, ed. (IRL Press, 1991) and Sambrook *et al.*, *supra.*

Methods of transfection are known to the ordinarily skilled artisan, for example, $CaPO_4$ treatment and electroporation. Depending on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook *et al.*, *supra*, or electroporation is generally used for prokaryotes or other cells that contain substantial cell-wall barriers. Infection with *Agrobacterium tumefaciens* is used for transformation of certain plant cells, as described by Shaw *et al.*, Gene, 23: 315 (1983) and WO 89/05859 published 29 June 1989. For mammalian cells without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, Virology, 52:456-457 (1978) can be employed. General aspects of mammalian cell host system transformations have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van Solingen *et al.*, J. Bact., 130: 946 (1977) and Hsiao *et al.*, Proc. Natl. Acad. Sci. (USA), 76: 3829 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, *e.g.*, polybrene or polyornithine, may also be used. For various techniques for

transforming mammalian cells, *see*, Keown *et al.*, Methods in Enzymology, 185: 527-537 (1990) and Mansour *et al.*, Nature, 336: 348-352 (1988).

Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include, but are not limited to, eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325); and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as *Escherichia*, *e.g.*, *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, *e.g.*, *Salmonella typhimurium*, *Serratia*, *e.g.*, *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (*e.g.*, *B. licheniformis* 41P disclosed in DD 266,710 published 12 April 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype *tonA* ; *E. coli* W3110 strain 9E4, which has the complete genotype *tonA ptr3*; *E. coli* W3110 strain 27C7 (ATCC 55,244), which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT kan^r*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7 ilvG kan^r*; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, *e.g.*, PCR or other nucleic acid polymerase reactions, are suitable.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for vectors encoding the PRO polypeptide. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* (Beach and Nurse, Nature, 290: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 4,943,529; Fleer *et al.*, Bio/Technology, 9: 968-975 (1991)) such as, *e.g.*, *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt *et al.*, J. Bacteriol., 737 [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickeramii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilarum* (ATCC 36,906; Van den Berg *et al.*, Bio/Technology, 8: 135 (1990)), *K. thermotolerans*, and *K. marxianus; yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreekrishna *et al.*, J. Basic Microbiol., 28: 265-278 [1988]); *Candida; Trichoderma reesia* (EP 244,234); *Neurospora crassa* (Case *et al.*, Proc. Natl. Acad. Sci. USA, 76: 5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, *e.g.*, *Neurospora, Penicillium, Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance *et al.*, Biochem. Biophys. Res. Commun., 112: 284-289 [1983]; Tilburn *et al.*, Gene, 26: 205-221 [1983]; Yelton *et al.*, Proc. Natl. Acad. Sci. USA, 81: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, EMBO J., 4: 475-479 [1985]). Methylotropic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula, Candida, Kloeckera, Pichia, Saccharomyces,*

Torulopsis, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, The Biochemistry of Methylotrophs, 269 (1982).

Suitable host cells for the expression of nucleic acid encoding glycosylated PRO polypeptides are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as Drosophila S2 and Spodoptera Sf9, as well as plant cells. Examples of useful mammalian host cell lines include Chinese hamster ovary (CHO) and COS cells. More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham *et al.*, J. Gen. Virol., 36: 59 (1977)); Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, Proc. Natl. Acad. Sci. USA, 77:4216 (1980)); mouse sertoli cells (TM4, Mather, Biol. Reprod., 23:243-251 (1980)); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor (MMT 060562, ATCC CCL51). The selection of the appropriate host cell is deemed to be within the skill in the art.

5.2.3.3. Selection and Use of a Replicable Vector

The nucleic acid (*e.g.*, cDNA or genomic DNA) encoding the PRO polypeptide may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally include, but are not limited to, one or more of a signal sequence if the sequence is to be secreted, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques that are known to the skilled artisan.

The PRO polypeptide may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the DNA encoding the PRO polypeptide that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, *e.g.*, the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces* α-factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2μ plasmid origin

is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV, or BPV) are useful for cloning vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, *e.g.*, ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, *e.g.*, the gene encoding D-alanine racemase for *Bacilli*.

An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the nucleic acid encoding the PRO polypeptide such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described by Urlaub *et al.*, Proc. Natl. Acad. Sci. USA, 77: 4216 (1980). A suitable selection gene for use in yeast is the *trp*1 gene present in the yeast plasmid YRp7. Stinchcomb *et al.*, Nature, 282: 39 (1979); Kingsman *et al.*, Gene, 7: 141 (1979); Tschemper *et al.*, Gene, 10: 157 (1980). The *trp*1 gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1. Jones, Genetics, 85: 12 (1977).

Expression and cloning vectors usually contain a promoter operably linked to the nucleic acid sequence encoding the PRO polypeptide to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the β-lactamase and lactose promoter systems (Chang *et al.*, Nature, 275: 615 (1978); Goeddel *et al.*, Nature, 281: 544 (1979)), alkaline phosphatase, a tryptophan (trp) promoter system (Goeddel, Nucleic Acids Res., 8: 4057 (1980); EP 36,776), and hybrid promoters such as the tac promoter (deBoer *et al.*, Proc. Natl. Acad. Sci. USA, 80: 21-25 (1983)). Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding the PRO polypeptide.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase (Hitzeman *et al.*, J. Biol. Chem., 255: 2073 (1980)) or other glycolytic enzymes (Hess *et al.*, J. Adv. Enzyme Reg., 7: 149 (1968); Holland, Biochemistry, 17: 4900 (1978)), such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

Other yeast promoters that are inducible promoters having the additional advantage of transcription controlled by growth conditions are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657.

PRO nucleic acid transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus, and Simian Virus 40 (SV40); by heterologous mammalian promoters, *e.g.*, the actin

promoter or an immunoglobulin promoter; and by heat-shock promoters, provided such promoters are compatible with the host cell systems.

Transcription of a DNA encoding the PRO polypeptide by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, α-fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the sequence coding for PRO polypeptides, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding the PRO polypeptide.

Still other methods, vectors, and host cells suitable for adaptation to the synthesis of the PRO polypeptide in recombinant vertebrate cell culture are described in Gething *et al.*, Nature, 293: 620-625 (1981); Mantei *et al.*, Nature, 281: 40-46 (1979); EP 117,060; and EP 117,058.

5.2.3.4. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA (Thomas, Proc. Natl. Acad. Sci. USA, 77:5201-5205 (1980)), dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native-sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to DNA encoding the PRO polypeptide and encoding a specific antibody epitope.

5.2.3.5. Purification of PRO Polypeptides

Forms of PRO polypeptides may be recovered from culture medium or from host cell lysates. If

membrane-bound, it can be released from the membrane using a suitable detergent solution (*e.g.*, TRITON-X™ 100) or by enzymatic cleavage. Cells employed in expression of nucleic acid encoding the PRO polypeptide can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell-lysing agents. It may be desired to purify the PRO polypeptide from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the PRO polypeptide. Various methods of protein purification may be employed and such methods are known in the art and described, for example, in Deutscher, Methods in Enzymology, 182 (1990); Scopes, Protein Purification: Principles and Practice (Springer-Verlag: New York, 1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular PRO polypeptide produced.

5.2.4. Uses of PRO Polypeptides

5.2.4.1. Assays for Cardiovascular, Endothelial, and Angiogenic Activity

Various assays can be used to test the polypeptide herein for cardiovascular, endothelial, and angiogenic activity. Such assays include those provided in the Examples below.

Assays for testing for endothelin antagonist activity, as disclosed in U.S. Pat. No. 5,773,414, include a rat heart ventricle binding assay where the polypeptide is tested for its ability to inhibit iodinized endothelin-1 binding in a receptor assay, an endothelin receptor binding assay testing for intact cell binding of radiolabeled endothelin-1 using rabbit renal artery vascular smooth muscle cells, an inositol phosphate accumulation assay where functional activity is determined in Rat-1 cells by measuring intra-cellular levels of second messengers, an arachidonic acid release assay that measures the ability of added compounds to reduce endothelin-stimulated arachidonic acid release in cultured vascular smooth muscles, *in vitro* (isolated vessel) studies using endothelium from male New Zealand rabbits, and *in vivo* studies using male Sprague-Dawley rats.

Assays for tissue generation activity include, without limitation, those described in WO 95/16035 (bone, cartilage, tendon); WO 95/05846 (nerve, neuronal), and WO 91/07491 (skin, endothelium).

Assays for wound-healing activity include, for example, those described in Winter, Epidermal Wound Healing, Maibach, HI and Rovee, DT, eds. (Year Book Medical Publishers, Inc., Chicago), pp. 71-112, as modified by the article of Eaglstein and Mertz, J. Invest. Dermatol., 71: 382-384 (1978).

An assay to screen for a test molecule relating to a PRO polypeptide that binds an endothelin B_1 (ETB_1) receptor polypeptide and modulates signal transduction activity involves providing a host cell transformed with a DNA encoding endothelin B_1 receptor polypeptide, exposing the cells to the test candidate, and measuring endothelin B_1 receptor signal transduction activity, as described, *e.g.*, in U.S. Pat. No. 5,773,223.

There are several cardiac hypertrophy assays. *In vitro* assays include induction of spreading of adult rat cardiac myocytes. In this assay, ventricular myocytes are isolated from a single (male Sprague-Dawley) rat,

essentially following a modification of the procedure described in detail by Piper *et al.*, "Adult ventricular rat heart muscle cells" in Cell Culture Techniques in Heart and Vessel Research, H.M. Piper, ed. (Berlin: Springer-Verlag, 1990), pp. 36-60. This procedure permits the isolation of adult ventricular myocytes and the long-term culture of these cells in the rod-shaped phenotype. Phenylephrine and Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) have been shown to induce a spreading response in these adult cells. The inhibition of myocyte spreading induced by $PGF_{2\alpha}$ or $PGF_{2\alpha}$ analogs (*e.g.*, fluprostenol) and phenylephrine by various potential inhibitors of cardiac hypertrophy is then tested.

One example of an *in vivo* assay is a test for inhibiting cardiac hypertrophy induced by fluprostenol *in vivo*. This pharmacological model tests the ability of the PRO polypeptide to inhibit cardiac hypertrophy induced in rats (*e.g.*, male Wistar or Sprague-Dawley) by subcutaneous injection of fluprostenol (an agonist analog of $PGF_{2\alpha}$). It is known that rats with pathologic cardiac hypertrophy induced by myocardial infarction have chronically elevated levels of extractable $PGF_{2\alpha}$ in their myocardium. Lai *et al.*, Am. J. Physiol. (Heart Circ. Physiol.), 271: H2197-H2208 (1996). Accordingly, factors that can inhibit the effects of fluprostenol on myocardial growth *in vivo* are potentially useful for treating cardiac hypertrophy. The effects of the PRO polypeptide on cardiac hypertrophy are determined by measuring the weight of heart, ventricles, and left ventricle (normalized by body weight) relative to fluprostenol-treated rats not receiving the PRO polypeptide.

Another example of an *in vivo* assay is the pressure-overload cardiac hypertrophy assay. For *in vivo* testing it is common to induce pressure-overload cardiac hypertrophy by constriction of the abdominal aorta of test animals. In a typical protocol, rats (*e.g.*, male Wistar or Sprague-Dawley) are treated under anesthesia, and the abdominal aorta of each rat is narrowed down just below the diaphragm. Beznak M., Can. J. Biochem. Physiol., 33: 985-94 (1955). The aorta is exposed through a surgical incision, and a blunted needle is placed next to the vessel. The aorta is constricted with a ligature of silk thread around the needle, which is immediately removed and which reduces the lumen of the aorta to the diameter of the needle. This approach is described, for example, in Rossi *et al.*, Am. Heart J., 124: 700-709 (1992) and O'Rourke and Reibel, P.S.E.M.B., 200: 95-100 (1992).

In yet another *in vivo* assay, the effect on cardiac hypertrophy following experimentally induced myocardial infarction (MI) is measured. Acute MI is induced in rats by left coronary artery ligation and confirmed by electrocardiographic examination. A sham-operated group of animals is also prepared as control animals. Earlier data have shown that cardiac hypertrophy is present in the group of animals with MI, as evidenced by an 18% increase in heart weight-to-body weight ratio. Lai *et al., supra.* Treatment of these animals with candidate blockers of cardiac hypertrophy, *e.g.*, the PRO polypeptide, provides valuable information about the therapeutic potential of the candidates tested. One further such assay test for induction of cardiac hypertrophy is disclosed in U.S. Pat. No. 5,773,415, using Sprague-Dawley rats.

For cancer, a variety of well-known animal models can be used to further understand the role of the genes identified herein in the development and pathogenesis of tumors, and to test the efficacy of candidate therapeutic agents, including antibodies and other antagonists of native PRO polypeptides, such as small-molecule antagonists. The *in vivo* nature of such models makes them particularly predictive of responses in human patients. Animal models of tumors and cancers (*e.g.*, breast cancer, colon cancer, prostate cancer, lung cancer, etc.) include both non-recombinant and recombinant (transgenic) animals. Non-recombinant animal models include, for example,

rodent, *e.g.*, murine models. Such models can be generated by introducing tumor cells into syngeneic mice using standard techniques, *e.g.*, subcutaneous injection, tail vein injection, spleen implantation, intraperitoneal implantation, implantation under the renal capsule, or orthopin implantation, *e.g.*, colon cancer cells implanted in colonic tissue. *See*, *e.g.*, PCT publication No. WO 97/33551, published September 18, 1997. Probably the most often used animal species in oncological studies are immunodeficient mice and, in particular, nude mice. The observation that the nude mouse with thymic hypo/aplasia could successfully act as a host for human tumor xenografts has lead to its widespread use for this purpose. The autosomal recessive *nu* gene has been introduced into a very large number of distinct congenic strains of nude mouse, including, for example, ASW, A/He, AKR, BALB/c, B10.LP, C17, C3H, C57BL, C57, CBA, DBA, DDD, I/st, NC, NFR, NFS, NFS/N, NZB, NZC, NZW, P, RIII, and SJL. In addition, a wide variety of other animals with inherited immunological defects other than the nude mouse have been bred and used as recipients of tumor xenografts. For further details *see*, *e.g.*, The Nude Mouse in Oncology Research, E. Boven and B. Winograd, eds. (CRC Press, Inc., 1991).

The cells introduced into such animals can be derived from known tumor/cancer cell lines, such as any of the above-listed tumor cell lines, and, for example, the B104-1-1 cell line (stable NIH-3T3 cell line transfected with the *neu* protooncogene); *ras*-transfected NIH-3T3 cells; Caco-2 (ATCC HTB-37); or a moderately well-differentiated grade II human colon adenocarcinoma cell line, HT-29 (ATCC HTB-38); or from tumors and cancers. Samples of tumor or cancer cells can be obtained from patients undergoing surgery, using standard conditions involving freezing and storing in liquid nitrogen. Karmali *et al.*, Br. J. Cancer, 48: 689-696 (1983).

Tumor cells can be introduced into animals such as nude mice by a variety of procedures. The subcutaneous (s.c.) space in mice is very suitable for tumor implantation. Tumors can be transplanted s.c. as solid blocks, as needle biopsies by use of a trochar, or as cell suspensions. For solid-block or trochar implantation, tumor tissue fragments of suitable size are introduced into the s.c. space. Cell suspensions are freshly prepared from primary tumors or stable tumor cell lines, and injected subcutaneously. Tumor cells can also be injected as subdermal implants. In this location, the inoculum is deposited between the lower part of the dermal connective tissue and the s.c. tissue.

Animal models of breast cancer can be generated, for example, by implanting rat neuroblastoma cells (from which the *neu* oncogene was initially isolated), or *neu*-transformed NIH-3T3 cells into nude mice, essentially as described by Drebin *et al.* Proc. Nat. Acad. Sci. USA, 83: 9129-9133 (1986).

Similarly, animal models of colon cancer can be generated by passaging colon cancer cells in animals, *e.g.*, nude mice, leading to the appearance of tumors in these animals. An orthotopic transplant model of human colon cancer in nude mice has been described, for example, by Wang *et al.*, Cancer Research, 54: 4726-4728 (1994) and Too *et al.*, Cancer Research, 55: 681-684 (1995). This model is based on the so-called "METAMOUSE™" sold by AntiCancer, Inc., (San Diego, California).

Tumors that arise in animals can be removed and cultured *in vitro*. Cells from the *in vitro* cultures can then be passaged to animals. Such tumors can serve as targets for further testing or drug screening. Alternatively, the tumors resulting from the passage can be isolated and RNA from pre-passage cells and cells isolated after one or more rounds of passage analyzed for differential expression of genes of interest. Such passaging techniques can

be performed with any known tumor or cancer cell lines.

For example, Meth A, CMS4, CMS5, CMS21, and WEHI-164 are chemically induced fibrosarcomas of BALB/c female mice (DeLeo *et al.*, J. Exp. Med., 146: 720 (1977)), which provide a highly controllable model system for studying the anti-tumor activities of various agents. Palladino *et al.*, J. Immunol., 138: 4023-4032 (1987). Briefly, tumor cells are propagated *in vitro* in cell culture. Prior to injection into the animals, the cell lines are washed and suspended in buffer, at a cell density of about 10×10^6 to 10×10^7 cells/ml. The animals are then infected subcutaneously with 10 to 100 µl of the cell suspension, allowing one to three weeks for a tumor to appear.

In addition, the Lewis lung (3LL) carcinoma of mice, which is one of the most thoroughly studied experimental tumors, can be used as an investigational tumor model. Efficacy in this tumor model has been correlated with beneficial effects in the treatment of human patients diagnosed with small-cell carcinoma of the lung (SCCL). This tumor can be introduced in normal mice upon injection of tumor fragments from an affected mouse or of cells maintained in culture. Zupi *et al.*, Br. J. Cancer, 41: suppl. 4, 30 (1980). Evidence indicates that tumors can be started from injection of even a single cell and that a very high proportion of infected tumor cells survive. For further information about this tumor model *see*, Zacharski, Haemostasis, 16: 300-320 (1986).

One way of evaluating the efficacy of a test compound in an animal model with an implanted tumor is to measure the size of the tumor before and after treatment. Traditionally, the size of implanted tumors has been measured with a slide caliper in two or three dimensions. The measure limited to two dimensions does not accurately reflect the size of the tumor; therefore, it is usually converted into the corresponding volume by using a mathematical formula. However, the measurement of tumor size is very inaccurate. The therapeutic effects of a drug candidate can be better described as treatment-induced growth delay and specific growth delay. Another important variable in the description of tumor growth is the tumor volume doubling time. Computer programs for the calculation and description of tumor growth are also available, such as the program reported by Rygaard and Spang-Thomsen, Proc. 6th Int. Workshop on Immune-Deficient Animals, Wu and Sheng eds. (Basel, 1989), p. 301. It is noted, however, that necrosis and inflammatory responses following treatment may actually result in an increase in tumor size, at least initially. Therefore, these changes need to be carefully monitored, by a combination of a morphometric method and flow cytometric analysis.

Further, recombinant (transgenic) animal models can be engineered by introducing the coding portion of the PRO gene identified herein into the genome of animals of interest, using standard techniques for producing transgenic animals. Animals that can serve as a target for transgenic manipulation include, without limitation, mice, rats, rabbits, guinea pigs, sheep, goats, pigs, and non-human primates, *e.g.*, baboons, chimpanzees and monkeys. Techniques known in the art to introduce a transgene into such animals include pronucleic microinjection (U.S. Patent No. 4,873,191); retrovirus-mediated gene transfer into germ lines (*e.g.*, Van der Putten *et al.*, Proc. Natl. Acad. Sci. USA, 82: 6148-615 (1985)); gene targeting in embryonic stem cells (Thompson *et al.*, Cell, 56: 313-321 (1989)); electroporation of embryos (Lo, Mol. Cell. Biol., 3: 1803-1814 (1983)); and sperm-mediated gene transfer. Lavitrano *et al.*, Cell, 57: 717-73 (1989). For a review, *see* for example, U.S. Patent No. 4,736,866.

For the purpose of the present invention, transgenic animals include those that carry the transgene only in part of their cells ("mosaic animals"). The transgene can be integrated either as a single transgene, or in

concatamers, *e.g.*, head-to-head or head-to-tail tandems. Selective introduction of a transgene into a particular cell type is also possible by following, for example, the technique of Lasko *et al.*, Proc. Natl. Acad. Sci. USA, 89: 6232-636 (1992). The expression of the transgene in transgenic animals can be monitored by standard techniques. For example, Southern blot analysis or PCR amplification can be used to verify the integration of the transgene. The level of mRNA expression can then be analyzed using techniques such as *in situ* hybridization, Northern blot analysis, PCR, or immunocytochemistry. The animals are further examined for signs of tumor or cancer development.

Alternatively, "knock-out" animals can be constructed that have a defective or altered gene encoding a PRO polypeptide identified herein, as a result of homologous recombination between the endogenous gene encoding the PRO polypeptide and altered genomic DNA encoding the same polypeptide introduced into an embryonic cell of the animal. For example, cDNA encoding a particular PRO polypeptide can be used to clone genomic DNA encoding that polypeptide in accordance with established techniques. A portion of the genomic DNA encoding a particular PRO polypeptide can be deleted or replaced with another gene, such as a gene encoding a selectable marker that can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector. *See, e.g.*, Thomas and Capecchi, Cell, 51: 503 (1987) for a description of homologous recombination vectors. The vector is introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected. *See, e.g.*, Li *et al.*, Cell, 69: 915 (1992). The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse or rat) to form aggregation chimeras. *See, e.g.*, Bradley, in Teratocarcinomas and Embryonic Stem Cells: A Practical Approach, E. J. Robertson, ed. (IRL: Oxford, 1987), pp. 113-152. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock-out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized, for instance, by their ability to defend against certain pathological conditions and by their development of pathological conditions due to absence of the PRO polypeptide.

The efficacy of antibodies specifically binding the PRO polypeptides identified herein, and other drug candidates, can be tested also in the treatment of spontaneous animal tumors. A suitable target for such studies is the feline oral squamous cell carcinoma (SCC). Feline oral SCC is a highly invasive, malignant tumor that is the most common oral malignancy of cats, accounting for over 60% of the oral tumors reported in this species. It rarely metastasizes to distant sites, although this low incidence of metastasis may merely be a reflection of the short survival times for cats with this tumor. These tumors are usually not amenable to surgery, primarily because of the anatomy of the feline oral cavity. At present, there is no effective treatment for this tumor. Prior to entry into the study, each cat undergoes complete clinical examination and biopsy, and is scanned by computed tomography (CT). Cats diagnosed with sublingual oral squamous cell tumors are excluded from the study. The tongue can become paralyzed as a result of such tumor, and even if the treatment kills the tumor, the animals may not be able to feed themselves. Each cat is treated repeatedly, over a longer period of time. Photographs of the tumors will be taken daily during the treatment period, and at each subsequent recheck. After treatment, each cat undergoes another CT

scan. CT scans and thoracic radiograms are evaluated every 8 weeks thereafter. The data are evaluated for differences in survival, response, and toxicity as compared to control groups. Positive response may require evidence of tumor regression, preferably with improvement of quality of life and/or increased life span.

In addition, other spontaneous animal tumors, such as fibrosarcoma, adenocarcinoma, lymphoma, chondroma, or leiomyosarcoma of dogs, cats, and baboons can also be tested. Of these, mammary adenocarcinoma in dogs and cats is a preferred model as its appearance and behavior are very similar to those in humans. However, the use of this model is limited by the rare occurrence of this type of tumor in animals.

Other *in vitro* and *in vivo* cardiovascular, endothelial, and angiogenic tests known in the art are also suitable herein.

5.2.4.2. Tissue Distribution

The results of the cardiovascular, endothelial, and angiogenic assays herein can be verified by further studies, such as by determining mRNA expression in various human tissues.

As noted before, gene amplification and/or gene expression in various tissues may be measured by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA (Thomas, Proc. Natl. Acad. Sci. USA, 77:5201-5205 (1980)), dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes.

Gene expression in various tissues, alternatively, may be measured by immunological methods, such as immunohistochemical staining of tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native-sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to PRO DNA and encoding a specific antibody epitope. General techniques for generating antibodies, and special protocols for *in situ* hybridization are provided hereinbelow.

5.2.4.3. Antibody Binding Studies

The results of the cardiovascular, endothelial, and angiogenic study can be further verified by antibody binding studies, in which the ability of anti-PRO antibodies to inhibit the effect of the PRO polypeptides on endothelial cells or other cells used in the cardiovascular, endothelial, and angiogenic assays is tested. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies, the preparation of which will be described hereinbelow.

Antibody binding studies may be carried out in any known assay method, such as competitive binding assays, direct and indirect sandwich assays, and immunoprecipitation assays. Zola, Monoclonal Antibodies: A Manual of Techniques (CRC Press, Inc., 1987), pp.147-158.

Competitive binding assays rely on the ability of a labeled standard to compete with the test sample analyte for binding with a limited amount of antibody. The amount of target protein in the test sample is inversely proportional to the amount of standard that becomes bound to the antibodies. To facilitate determining the amount of standard that becomes bound, the antibodies preferably are insolubilized before or after the competition, so that the standard and analyte that are bound to the antibodies may conveniently be separated from the standard and analyte that remain unbound.

Sandwich assays involve the use of two antibodies, each capable of binding to a different immunogenic portion, or epitope, of the protein to be detected. In a sandwich assay, the test sample analyte is bound by a first antibody that is immobilized on a solid support, and thereafter a second antibody binds to the analyte, thus forming an insoluble three-part complex. *See, e.g.*, U.S. Pat. No. 4,376,110. The second antibody may itself be labeled with a detectable moiety (direct sandwich assays) or may be measured using an anti-immunoglobulin antibody that is labeled with a detectable moiety (indirect sandwich assay). For example, one type of sandwich assay is an ELISA assay, in which case the detectable moiety is an enzyme.

For immunohistochemistry, the tissue sample may be fresh or frozen or may be embedded in paraffin and fixed with a preservative such as formalin, for example.

5.2.4.4. Cell-Based Tumor Assays

Cell-based assays and animal models for cardiovascular, endothelial, and angiogenic disorders, such as tumors, can be used to verify the findings of a cardiovascular, endothelial, and angiogenic assay herein, and further to understand the relationship between the genes identified herein and the development and pathogenesis of undesirable cardiovascular, endothelial, and angiogenic cell growth. The role of gene products identified herein in the development and pathology of undesirable cardiovascular, endothelial, and angiogenic cell growth, *e.g.*, tumor cells, can be tested by using cells or cells lines that have been identified as being stimulated or inhibited by the PRO polypeptide herein. Such cells include, for example, those set forth in the Examples below.

In a different approach, cells of a cell type known to be involved in a particular cardiovascular, endothelial, and angiogenic disorder are transfected with the cDNAs herein, and the ability of these cDNAs to induce excessive growth or inhibit growth is analyzed. If the cardiovascular, endothelial, and angiogenic disorder is cancer, suitable tumor cells include, for example, stable tumor cell lines such as the B104-1-1 cell line (stable NIH-3T3 cell line transfected with the *neu* protooncogene) and *ras*-transfected NIH-3T3 cells, which can be transfected with the desired gene and monitored for tumorigenic growth. Such transfected cell lines can then be used to test the ability of poly- or monoclonal antibodies or antibody compositions to inhibit tumorigenic cell growth by exerting cytostatic or cytotoxic activity on the growth of the transformed cells, or by mediating antibody-dependent cellular cytotoxicity (ADCC). Cells transfected with the coding sequences of the genes identified herein can further be used to identify drug candidates for the treatment of cardiovascular, endothelial, and angiogenic disorders such as cancer.

In addition, primary cultures derived from tumors in transgenic animals (as described above) can be used in the cell-based assays herein, although stable cell lines are preferred. Techniques to derive continuous cell lines from transgenic animals are well known in the art. *See, e.g.*, Small *et al.*, Mol. Cell. Biol., 5: 642-648 (1985).

5.2.4.5. Gene Therapy

Described below are methods and compositions whereby disease symptoms may be ameliorated. Certain diseases are brought about, at least in part, by an excessive level of gene product, or by the presence of a gene product exhibiting an abnormal or excessive activity. As such, the reduction in the level and/or activity of such gene products would bring about the amelioration of such disease symptoms.

Alternatively, certain other diseases are brought about, at least in part, by the absence or reduction of the level of gene expression, or a reduction in the level of a gene product's activity. As such, an increase in the level of gene expression and/or the activity of such gene products would bring about the amelioration of such disease symptoms.

In some cases, the up-regulation of a gene in a disease state reflects a protective role for that gene product in responding to the disease condition. Enhancement of such a target gene's expression, or the activity of the target gene product, will reinforce the protective effect it exerts. Some disease states may result from an abnormally low level of activity of such a protective gene. In these cases also, an increase in the level of gene expression and/or the activity of such gene products would bring about the amelioration of such disease symptoms.

The PRO polypeptides described herein and polypeptidyl agonists and antagonists may be employed in accordance with the present invention by expression of such polypeptides *in vivo*, which is often referred to as gene therapy.

There are two major approaches to getting the nucleic acid (optionally contained in a vector) into the patient's cells: *in vivo* and *ex vivo*. For *in vivo* delivery the nucleic acid is injected directly into the patient, usually at the sites where the PRO polypeptide is required, *i.e.*, the site of synthesis of the PRO polypeptide, if known, and the site (*e.g.*, wound) where biological activity of the PRO polypeptide is needed. For *ex vivo* treatment, the patient's cells are removed, the nucleic acid is introduced into these isolated cells, and the modified cells are administered to the patient either directly or, for example, encapsulated within porous membranes that are implanted into the patient (*see, e.g.*, U.S. Pat. Nos. 4,892,538 and 5,283,187). There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or transferred *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, transduction, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. Transduction involves the association of a replication-defective, recombinant viral (preferably retroviral) particle with a cellular receptor, followed by introduction of the nucleic acids contained by the particle into the cell. A commonly used vector for *ex vivo* delivery of the gene is a retrovirus.

The currently preferred *in vivo* nucleic acid transfer techniques include transfection with viral or non-viral vectors (such as adenovirus, lentivirus, Herpes simplex I virus, or adeno-associated virus (AAV)) and lipid-based systems (useful lipids for lipid-mediated transfer of the gene are, for example, DOTMA, DOPE, and DC-Chol; *see, e.g.*, Tonkinson *et al.*, Cancer Investigation, 14(1): 54-65 (1996)). The most preferred vectors for use in gene therapy are viruses, most preferably adenoviruses, AAV, lentiviruses, or retroviruses. A viral vector such as a retroviral vector includes at least one transcriptional promoter/enhancer or locus-defining element(s), or other

elements that control gene expression by other means such as alternate splicing, nuclear RNA export, or post-translational modification of messenger. In addition, a viral vector such as a retroviral vector includes a nucleic acid molecule that, when transcribed in the presence of a gene encoding the PRO polypeptide, is operably linked thereto and acts as a translation initiation sequence. Such vector constructs also include a packaging signal, long terminal repeats (LTRs) or portions thereof, and positive and negative strand primer binding sites appropriate to the virus used (if these are not already present in the viral vector). In addition, such vector typically includes a signal sequence for secretion of the PRO polypeptide from a host cell in which it is placed. Preferably the signal sequence for this purpose is a mammalian signal sequence, most preferably the native signal sequence for the PRO polypeptide. Optionally, the vector construct may also include a signal that directs polyadenylation, as well as one or more restriction sites and a translation termination sequence. By way of example, such vectors will typically include a 5' LTR, a tRNA binding site, a packaging signal, an origin of second-strand DNA synthesis, and a 3' LTR or a portion thereof. Other vectors can be used that are non-viral, such as cationic lipids, polylysine, and dendrimers.

In some situations, it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell-surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins that bind to a cell-surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, *e.g.*, capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins that undergo internalization in cycling, and proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu *et al.*, J. Biol. Chem., 262: 4429-4432 (1987); and Wagner *et al.*, Proc. Natl. Acad. Sci. USA, 87: 3410-3414 (1990). For a review of the currently known gene marking and gene therapy protocols, *see*, Anderson *et al.*, Science, 256: 808-813 (1992). *See* also WO 93/25673 and the references cited therein.

Suitable gene therapy and methods for making retroviral particles and structural proteins can be found in, *e.g.*, U.S. Pat. No. 5,681,746.

5.2.4.6. Use of Gene as a Diagnostic

This invention is also related to the use of the gene encoding the PRO polypeptide as a diagnostic. Detection of a mutated form of the PRO polypeptide will allow a diagnosis of a cardiovascular, endothelial, and angiogenic disease or a susceptibility to a cardiovascular, endothelial, and angiogenic disease, such as a tumor, since mutations in the PRO polypeptide may cause tumors.

Individuals carrying mutations in the genes encoding a human PRO polypeptide may be detected at the DNA level by a variety of techniques. Nucleic acids for diagnosis may be obtained from a patient's cells, such as from blood, urine, saliva, tissue biopsy, and autopsy material. The genomic DNA may be used directly for detection or may be amplified enzymatically by using PCR (Saiki *et al.*, Nature, 324: 163-166 (1986)) prior to analysis. RNA or cDNA may also be used for the same purpose. As an example, PCR primers complementary to the nucleic acid encoding the PRO polypeptide can be used to identify and analyze the PRO polypeptide mutations. For example, deletions and insertions can be detected by a change in size of the amplified product in comparison to the normal

genotype. Point mutations can be identified by hybridizing amplified DNA to radiolabeled RNA encoding the PRO polypeptide, or alternatively, radiolabeled antisense DNA sequences encoding the PRO polypeptide. Perfectly matched sequences can be distinguished from mismatched duplexes by RNase A digestion or by differences in melting temperatures.

Genetic testing based on DNA sequence differences may be achieved by detection of alteration in electrophoretic mobility of DNA fragments in gels with or without denaturing agents. Small sequence deletions and insertions can be visualized by high resolution gel electrophoresis. DNA fragments of different sequences may be distinguished on denaturing formamidine gradient gels in which the mobilities of different DNA fragments are retarded in the gel at different positions according to their specific melting or partial melting temperatures. *See, e.g.*, Myers *et al.*, Science, 230: 1242 (1985).

Sequence changes at specific locations may also be revealed by nuclease protection assays, such as RNase and S1 protection or the chemical cleavage method, for example, Cotton *et al.*, Proc. Natl. Acad. Sci. USA, 85: 4397-4401 (1985).

Thus, the detection of a specific DNA sequence may be achieved by methods such as hybridization, RNase protection, chemical cleavage, direct DNA sequencing, or the use of restriction enzymes, *e.g.*, restriction fragment length polymorphisms (RFLP), and Southern blotting of genomic DNA.

5.2.4.7. Use to Detect PRO Polypeptide Levels

In addition to more conventional gel-electrophoresis and DNA sequencing, mutations can also be detected by *in situ* analysis.

Expression of nucleic acid encoding the PRO polypeptide may be linked to vascular disease or neovascularization associated with tumor formation. If the PRO polypeptide has a signal sequence and the mRNA is highly expressed in endothelial cells and to a lesser extent in smooth muscle cells, this indicates that the PRO polypeptide is present in serum. Accordingly, an anti-PRO polypeptide antibody could be used to diagnose vascular disease or neovascularization associated with tumor formation, since an altered level of this PRO polypeptide may be indicative of such disorders.

A competition assay may be employed wherein antibodies specific to the PRO polypeptide are attached to a solid support and the labeled PRO polypeptide and a sample derived from the host are passed over the solid support and the amount of label detected attached to the solid support can be correlated to a quantity of the PRO polypeptide in the sample.

5.2.4.8. Chromosome Mapping

The sequences of the present invention are also valuable for chromosome identification. The sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome. Moreover, there is a current need for identifying particular sites on the chromosome. Few chromosome marking reagents based on actual sequence data (repeat polymorphisms) are presently available for marking chromosomal location. The mapping of DNAs to chromosomes according to the present invention is an important first step in

correlating those sequences with genes associated with disease.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the cDNA. Computer analysis for the 3'- untranslated region is used to rapidly select primers that do not span more than one exon in the genomic DNA, thus complicating the amplification process. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the primer will yield an amplified fragment.

PCR mapping of somatic cell hybrids is a rapid procedure for assigning a particular DNA to a particular chromosome. Using the present invention with the same oligonucleotide primers, sublocalization can be achieved with panels of fragments from specific chromosomes or pools of large genomic clones in an analogous manner. Other mapping strategies that can similarly be used to map to its chromosome include *in situ* hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome-specific cDNA libraries.

Fluorescence *in situ* hybridization (FISH) of a cDNA clone to a metaphase chromosomal spread can be used to provide a precise chromosomal location in one step. This technique can be used with cDNA as short as 500 or 600 bases; however, clones larger than 2,000 bp have a higher likelihood of binding to a unique chromosomal location with sufficient signal intensity for simple detection. FISH requires use of the clones from which the gene encoding the PRO polypeptide was derived, and the longer the better. For example, 2,000 bp is good, 4,000 bp is better, and more than 4,000 is probably not necessary to get good results a reasonable percentage of the time. For a review of this technique, *see*, Verma *et al.*, Human Chromosomes: a Manual of Basic Techniques (Pergamon Press, New York, 1988).

Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. Such data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available online through Johns Hopkins University Welch Medical Library). The relationship between genes and diseases that have been mapped to the same chromosomal region is then identified through linkage analysis (coinheritance of physically adjacent genes).

Next, it is necessary to determine the differences in the cDNA or genomic sequence between affected and unaffected individuals. If a mutation is observed in some or all of the affected individuals but not in any normal individuals, then the mutation is likely to be the causative agent of the disease.

With current resolution of physical mapping and genetic mapping techniques, a cDNA precisely localized to a chromosomal region associated with the disease could be one of between 50 and 500 potential causative genes. (This assumes 1 megabase mapping resolution and one gene per 20 kb).

5.2.4.9. Screening Assays for Drug Candidates

This invention encompasses methods of screening compounds to identify those that mimic the PRO polypeptide (agonists) or prevent the effect of the PRO polypeptide (antagonists). Screening assays for antagonist drug candidates are designed to identify compounds that bind or complex with the PRO polypeptide encoded by the genes identified herein, or otherwise interfere with the interaction of the encoded polypeptides with other

cellular proteins. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates.

The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays, and cell-based assays, which are well characterized in the art.

All assays for antagonists are common in that they call for contacting the drug candidate with a PRO polypeptide encoded by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the PRO polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, *e.g.*, on a microtiter plate, by covalent or non-covalent attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the PRO polypeptide and drying. Alternatively, an immobilized antibody, *e.g.*, a monoclonal antibody, specific for the PRO polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized component, *e.g.*, the coated surface containing the anchored component. When the reaction is complete, the non-reacted components are removed, *e.g.*, by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labeled antibody specifically binding the immobilized complex.

If the candidate compound interacts with but does not bind to a particular PRO polypeptide encoded by a gene identified herein, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, *e.g.*, cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers (Fields and Song, Nature (London), 340: 245-246 (1989); Chien *et al.*, Proc. Natl. Acad. Sci. USA, 88: 9578-9582 (1991)) as disclosed by Chevray and Nathans, Proc. Natl. Acad. Sci. USA, 89: 5789-5793 (1991). Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, the other one functioning as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a GAL1-*lacZ* reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for β-galactosidase. A complete kit (MATCHMAKER™) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

Compounds that interfere with the interaction of a gene encoding a PRO polypeptide identified herein and other intra- or extracellular components can be tested as follows: usually a reaction mixture is prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

If the PRO polypeptide has the ability to stimulate the proliferation of endothelial cells in the presence of the co-mitogen ConA, then one example of a screening method takes advantage of this ability. Specifically, in the proliferation assay, human umbilical vein endothelial cells are obtained and cultured in 96-well flat-bottomed culture plates (Costar, Cambridge, MA) and supplemented with a reaction mixture appropriate for facilitating proliferation of the cells, the mixture containing Con-A (Calbiochem, La Jolla, CA). Con-A and the compound to be screened are added and after incubation at 37°C, cultures are pulsed with ^{3}-H-thymidine and harvested onto glass fiber filters (phD; Cambridge Technology, Watertown, MA). Mean ^{3}-H- thymidine incorporation (cpm) of triplicate cultures is determined using a liquid scintillation counter (Beckman Instruments, Irvine, CA). Significant ^{3}-(H)-thymidine incorporation indicates stimulation of endothelial cell proliferation.

To assay for antagonists, the assay described above is performed; however, in this assay the PRO polypeptide is added along with the compound to be screened and the ability of the compound to inhibit ^{3}-(H)thymidine incorporation in the presence of the PRO polypeptide indicates that the compound is an antagonist to the PRO polypeptide. Alternatively, antagonists may be detected by combining the PRO polypeptide and a potential antagonist with membrane-bound PRO polypeptide receptors or recombinant receptors under appropriate conditions for a competitive inhibition assay. The PRO polypeptide can be labeled, such as by radioactivity, such that the number of PRO polypeptide molecules bound to the receptor can be used to determine the effectiveness of the potential antagonist. The gene encoding the receptor can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting. Coligan *et al.*, Current Protocols in Immun., 1(2): Chapter 5 (1991). Preferably, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the PRO polypeptide and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the PRO polypeptide. Transfected cells that are grown on glass slides are exposed to the labeled PRO polypeptide. The PRO polypeptide can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase. Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an interactive sub-pooling and re-screening process, eventually yielding a single clone that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled PRO polypeptide can be photoaffinity-linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is

resolved by PAGE and exposed to X-ray film. The labeled complex containing the receptor can be excised, resolved into peptide fragments, and subjected to protein micro-sequencing. The amino acid sequence obtained from micro-sequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the gene encoding the putative receptor.

In another assay for antagonists, mammalian cells or a membrane preparation expressing the receptor would be incubated with the labeled PRO polypeptide in the presence of the candidate compound. The ability of the compound to enhance or block this interaction could then be measured.

The compositions useful in the treatment of cardiovascular, endothelial, and angiogenic disorders include, without limitation, antibodies, small organic and inorganic molecules, peptides, phosphopeptides, antisense and ribozyme molecules, triple-helix molecules, etc., that inhibit the expression and/or activity of the target gene product.

More specific examples of potential antagonists include an oligonucleotide that binds to the fusions of immunoglobulin with a PRO polypeptide, and, in particular, antibodies including, without limitation, poly- and monoclonal antibodies and antibody fragments, single-chain antibodies, anti-idiotypic antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. Alternatively, a potential antagonist may be a closely related protein, for example, a mutated form of the PRO polypeptide that recognizes the receptor but imparts no effect, thereby competitively inhibiting the action of the PRO polypeptide.

Another potential PRO polypeptide antagonist is an antisense RNA or DNA construct prepared using antisense technology, where, *e.g.*, an antisense RNA or DNA molecule acts to block directly the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding portion of the polynucleotide sequence, which encodes the mature PRO polypeptides herein, is used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple helix - *see*, Lee *et al.*, Nucl. Acids Res., 6:3073 (1979); Cooney *et al.*, Science, 241: 456 (1988); Dervan *et al.*, Science, 251:1360 (1991)), thereby preventing transcription and the production of the PRO polypeptide. A sequence "complementary" to a portion of an RNA, as referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex helix formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the longer the hybridizing nucleic acid, the more base mismatches with an RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into the PRO polypeptide (antisense - Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression (CRC Press: Boca Raton, FL, 1988).

The antisense oligonucleotides can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger, *et al.*, 1989, *Proc. Natl. Acad. Sci. U.S.A.* 86:6553-6556; Lemaitre, *et al.*, 1987, *Proc. Natl. Acad. Sci. U.S.A.* 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, *e.g.*, PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, 1988, *BioTechniques* 6:958-976) or intercalating agents (see, *e.g.*, Zon, 1988, *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, *e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including but not limited to arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an α-anomeric oligonucleotide. An α-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β-units, the strands run parallel to each other (Gautier, *et al.*, 1987, *Nucl. Acids Res.* 15:6625-6641). The oligonucleotide is a 2'-0-methylribonucleotide (Inoue, *et al.*, 1987, *Nucl. Acids Res.* 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue, *et al.*, 1987, *FEBS Lett.* 215:327-330).

Oligonucleotides of the invention may be synthesized by standard methods known in the art, *e.g.*, by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein, *et al.* (1988, *Nucl. Acids Res.* 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin, *et al.*, 1988, *Proc. Natl. Acad. Sci. U.S.A.* 85:7448-7451), *etc.*

The oligonucleotides described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of the PRO polypeptide. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation-initiation site, *e.g.*, between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

Antisense RNA or DNA molecules are generally at least about 5 bases in length, about 10 bases in length, about 15 bases in length, about 20 bases in length, about 25 bases in length, about 30 bases in length, about 35 bases in length, about 40 bases in length, about 45 bases in length, about 50 bases in length, about 55 bases in length, about 60 bases in length, about 65 bases in length, about 70 bases in length, about 75 bases in length, about 80 bases in length, about 85 bases in length, about 90 bases in length, about 95 bases in length, about 100 bases in length, or more.

Potential antagonists further include small molecules that bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the PRO polypeptide, thereby blocking the normal biological activity of the PRO polypeptide. Examples of small molecules include, but are not limited to, small peptides or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.

Additional potential antagonists are ribozymes, which are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details *see, e.g.,* Rossi, Current Biology, 4: 469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy target gene mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions which form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Myers, 1995, *Molecular Biology and Biotechnology: A Comprehensive Desk Reference*, VCH Publishers, New York, (see especially Figure 4, page 833) and in Haseloff and Gerlach, 1988, *Nature*, 334:585-591, which is incorporated herein by reference in its entirety.

Preferably the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the target gene mRNA, *i.e.*, to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

The ribozymes of the present invention also include RNA endoribonucleases (hereinafter "Cech-type ribozymes") such as the one which occurs naturally in *Tetrahymena thermophila* (known as the IVS, or L-19 IVS RNA) and which has been extensively described by Thomas Cech and collaborators (Zaug, *et al.*, 1984, *Science*, 224:574-578; Zaug and Cech, 1986, *Science*, 231:470-475; Zaug, *et al.*, 1986, *Nature*, 324:429-433; published International patent application No. WO 88/04300 by University Patents Inc.; Been and Cech, 1986, *Cell*, 47:207-216). The Cech-type ribozymes have an eight base pair active site that hybridizes to a target RNA sequence

whereafter cleavage of the target RNA takes place. The invention encompasses those Cech-type ribozymes that target eight base-pair active site sequences that are present in the target gene.

As in the antisense approach, the ribozymes can be composed of modified oligonucleotides (*e.g.*, for improved stability, targeting, *etc.*) and should be delivered to cells that express the target gene *in vivo*. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous target gene messages and inhibit translation. Because ribozymes, unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details *see, e.g.*, PCT publication No. WO 97/33551, *supra*.

These small molecules can be identified by any one or more of the screening assays discussed hereinabove and/or by any other screening techniques well known for those skilled in the art.

5.2.4.10. Types of Cardiovascular, Endothelial, and Angiogenic Disorders to be Treated

The PRO polypeptides, or agonists or antagonists thereto, that have activity in the cardiovascular, angiogenic, and endothelial assays described herein, and/or whose gene product has been found to be localized to the cardiovascular system, are likely to have therapeutic uses in a variety of cardiovascular, endothelial, and angiogenic disorders, including systemic disorders that affect vessels, such as diabetes mellitus. Their therapeutic utility could include diseases of the arteries, capillaries, veins, and/or lymphatics. Examples of treatments hereunder include treating muscle wasting disease, treating osteoporosis, aiding in implant fixation to stimulate the growth of cells around the implant and therefore facilitate its attachment to its intended site, increasing IGF stability in tissues or in serum, if applicable, and increasing binding to the IGF receptor (since IGF has been shown *in vitro* to enhance human marrow erythroid and granulocytic progenitor cell growth).

The PRO polypeptides or agonists or antagonists thereto may also be employed to stimulate erythropoiesis or granulopoiesis, to stimulate wound healing or tissue regeneration and associated therapies concerned with re-growth of tissue, such as connective tissue, skin, bone, cartilage, muscle, lung, or kidney, to promote angiogenesis, to stimulate or inhibit migration of endothelial cells, and to proliferate the growth of vascular smooth muscle and endothelial cell production. The increase in angiogenesis mediated by the PRO polypeptide or agonist would be beneficial to ischemic tissues and to collateral coronary development in the heart subsequent to coronary stenosis. Antagonists are used to inhibit the action of such polypeptides, for example, to limit the production of excess connective tissue during wound healing or pulmonary fibrosis if the PRO polypeptide promotes such production. This would include treatment of acute myocardial infarction and heart failure.

Moreover, the present invention provides the treatment of cardiac hypertrophy, regardless of the underlying cause, by administering a therapeutically effective dose of the PRO polypeptide, or agonist or antagonist thereto. If the objective is the treatment of human patients, the PRO polypeptide preferably is recombinant human PRO

polypeptide (rhPRO polypeptide). The treatment for cardiac hypertrophy can be performed at any of its various stages, which may result from a variety of diverse pathologic conditions, including myocardial infarction, hypertension, hypertrophic cardiomyopathy, and valvular regurgitation. The treatment extends to all stages of the progression of cardiac hypertrophy, with or without structural damage of the heart muscle, regardless of the underlying cardiac disorder.

The decision of whether to use the molecule itself or an agonist thereof for any particular indication, as opposed to an antagonist to the molecule, would depend mainly on whether the molecule herein promotes cardiovascularization, genesis of endothelial cells, or angiogenesis or inhibits these conditions. For example, if the molecule promotes angiogenesis, an antagonist thereof would be useful for treatment of disorders where it is desired to limit or prevent angiogenesis. Examples of such disorders include vascular tumors such as haemangioma, tumor angiogenesis, neovascularization in the retina, choroid, or cornea, associated with diabetic retinopathy or premature infant retinopathy or macular degeneration and proliferative vitreoretinopathy, rheumatoid arthritis, Crohn's disease, atherosclerosis, ovarian hyperstimulation, psoriasis, endometriosis associated with neovascularization, restenosis subsequent to balloon angioplasty, scar tissue overproduction, for example, that seen in a keloid that forms after surgery, fibrosis after myocardial infarction, or fibrotic lesions associated with pulmonary fibrosis.

If, however, the molecule inhibits angiogenesis, it would be expected to be used directly for treatment of the above conditions.

On the other hand, if the molecule stimulates angiogenesis it would be used itself (or an agonist thereof) for indications where angiogenesis is desired such as peripheral vascular disease, hypertension, inflammatory vasculitides, Reynaud's disease and Reynaud's phenomenon, aneurysms, arterial restenosis, thrombophlebitis, lymphangitis, lymphedema, wound healing and tissue repair, ischemia reperfusion injury, angina, myocardial infarctions such as acute myocardial infarctions, chronic heart conditions, heart failure such as congestive heart failure, and osteoporosis.

If, however, the molecule inhibits angiogenesis, an antagonist thereof would be used for treatment of those conditions where angiogenesis is desired.

Specific types of diseases are described below, where the PRO polypeptide herein or agonists or antagonists thereof may serve as useful for vascular-related drug targeting or as therapeutic targets for the treatment or prevention of the disorders. Atherosclerosis is a disease characterized by accumulation of plaques of intimal thickening in arteries, due to accumulation of lipids, proliferation of smooth muscle cells, and formation of fibrous tissue within the arterial wall. The disease can affect large, medium, and small arteries in any organ. Changes in endothelial and vascular smooth muscle cell function are known to play an important role in modulating the accumulation and regression of these plaques.

Hypertension is characterized by raised vascular pressure in the systemic arterial, pulmonary arterial, or portal venous systems. Elevated pressure may result from or result in impaired endothelial function and/or vascular disease.

Inflammatory vasculitides include giant cell arteritis, Takayasu's arteritis, polyarteritis nodosa (including the microangiopathic form), Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, and a variety

of infectious-related vascular disorders (including Henoch-Schonlein prupura). Altered endothelial cell function has been shown to be important in these diseases.

Reynaud's disease and Reynaud's phenomenon are characterized by intermittent abnormal impairment of the circulation through the extremities on exposure to cold. Altered endothelial cell function has been shown to be important in this disease.

Aneurysms are saccular or fusiform dilatations of the arterial or venous tree that are associated with altered endothelial cell and/or vascular smooth muscle cells.

Arterial restenosis (restenosis of the arterial wall) may occur following angioplasty as a result of alteration in the function and proliferation of endothelial and vascular smooth muscle cells.

Thrombophlebitis and lymphangitis are inflammatory disorders of veins and lymphatics, respectively, that may result from, and/or in, altered endothelial cell function. Similarly, lymphedema is a condition involving impaired lymphatic vessels resulting from endothelial cell function.

The family of benign and malignant vascular tumors are characterized by abnormal proliferation and growth of cellular elements of the vascular system. For example, lymphangiomas are benign tumors of the lymphatic system that are congenital, often cystic, malformations of the lymphatics that usually occur in newborns. Cystic tumors tend to grow into the adjacent tissue. Cystic tumors usually occur in the cervical and axillary region. They can also occur in the soft tissue of the extremities. The main symptoms are dilated, sometimes reticular, structured lymphatics and lymphocysts surrounded by connective tissue. Lymphangiomas are assumed to be caused by improperly connected embryonic lymphatics or their deficiency. The result is impaired local lymph drainage. Griener *et al.*, Lymphology, 4: 140-144 (1971).

Another use for the PRO polypeptides herein or agonists or antagonists thereto is in the prevention of tumor angiogenesis, which involves vascularization of a tumor to enable it to growth and/or metastasize. This process is dependent on the growth of new blood vessels. Examples of neoplasms and related conditions that involve tumor angiogenesis include breast carcinomas, lung carcinomas, gastric carcinomas, esophageal carcinomas, colorectal carcinomas, liver carcinomas, ovarian carcinomas, thecomas, arrhenoblastomas, cervical carcinomas, endometrial carcinoma, endometrial hyperplasia, endometriosis, fibrosarcomas, choriocarcinoma, head and neck cancer, nasopharyngeal carcinoma, laryngeal carcinomas, hepatoblastoma, Kaposi's sarcoma, melanoma, skin carcinomas, hemangioma, cavernous hemangioma, hemangioblastoma, pancreas carcinomas, retinoblastoma, astrocytoma, glioblastoma, Schwannoma, oligodendroglioma, medulloblastoma, neuroblastomas, rhabdomyosarcoma, osteogenic sarcoma, leiomyosarcomas, urinary tract carcinomas, thyroid carcinomas, Wilm's tumor, renal cell carcinoma, prostate carcinoma, abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), and Meigs' syndrome.

Age-related macular degeneration (AMD) is a leading cause of severe visual loss in the elderly population. The exudative form of AMD is characterized by choroidal neovascularization and retinal pigment epithelial cell detachment. Because choroidal neovascularization is associated with a dramatic worsening in prognosis, the PRO polypeptide or agonist or antagonist thereto is expected to be useful in reducing the severity of AMD.

Healing of trauma such as wound healing and tissue repair is also a targeted use for the PRO polypeptides herein or their agonists or antagonists. Formation and regression of new blood vessels is essential for tissue healing and repair. This category includes bone, cartilage, tendon, ligament, and/or nerve tissue growth or regeneration, as well as wound healing and tissue repair and replacement, and in the treatment of burns, incisions, and ulcers. A PRO polypeptide or agonist or antagonist thereof that induces cartilage and/or bone growth in circumstances where bone is not normally formed has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a PRO polypeptide or agonist or antagonist thereof may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma-induced, or oncologic, resection-induced craniofacial defects, and also is useful in cosmetic plastic surgery.

PRO polypeptides or agonists or antagonists thereto may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a PRO polypeptide or agonist or antagonist thereto may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, or endothelium), muscle (smooth, skeletal, or cardiac), and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate.

A PRO polypeptide herein or agonist or antagonist thereto may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage. Also, the PRO polypeptide or agonist or antagonist thereto may be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells, or for inhibiting the growth of tissues described above.

A PRO polypeptide or agonist or antagonist thereto may also be used in the treatment of periodontal diseases and in other tooth-repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells, or induce differentiation of progenitors of bone-forming cells. A PRO polypeptide herein or an agonist or an antagonist thereto may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes, since blood vessels play an important role in the regulation of bone turnover and growth.

Another category of tissue regeneration activity that may be attributable to the PRO polypeptide herein or agonist or antagonist thereto is tendon/ligament formation. A protein that induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed has application in the healing of tendon or ligament tears, deformities, and other tendon or ligament defects in humans and other animals. Such a preparation may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. *De novo* tendon/ligament-like tissue formation induced by a composition of the PRO polypeptide herein or

agonist or antagonist thereto contributes to the repair of congenital, trauma-induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions herein may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions herein may also be useful in the treatment of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The PRO polypeptide or its agonist or antagonist may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.*, for the treatment of central and peripheral nervous system disease and neuropathies, as well as mechanical and traumatic disorders, that involve degeneration, death, or trauma to neural cells or nerve tissue. More specifically, a PRO polypeptide or its agonist or antagonist may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions that may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma, and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a PRO polypeptide herein or agonist or antagonist thereto.

Ischemia-reperfusion injury is another indication. Endothelial cell dysfunction may be important in both the initiation of, and in regulation of the sequelae of events that occur following ischemia-reperfusion injury.

Rheumatoid arthritis is a further indication. Blood vessel growth and targeting of inflammatory cells through the vasculature is an important component in the pathogenesis of rheumatoid and sero-negative forms of arthritis.

A PRO polypeptide or its agonist or antagonist may also be administered prophylactically to patients with cardiac hypertrophy, to prevent the progression of the condition, and avoid sudden death, including death of asymptomatic patients. Such preventative therapy is particularly warranted in the case of patients diagnosed with massive left ventricular cardiac hypertrophy (a maximal wall thickness of 35 mm or more in adults, or a comparable value in children), or in instances when the hemodynamic burden on the heart is particularly strong.

A PRO polypeptide or its agonist or antagonist may also be useful in the management of atrial fibrillation, which develops in a substantial portion of patients diagnosed with hypertrophic cardiomyopathy.

Further indications include angina, myocardial infarctions such as acute myocardial infarctions, and heart failure such as congestive heart failure. Additional non-neoplastic conditions include psoriasis, diabetic and other proliferative retinopathies including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, chronic inflammation, lung inflammation, nephrotic syndrome, preeclampsia, ascites, pericardial effusion (such as that associated with pericarditis), and pleural effusion.

In view of the above, the PRO polypeptides or agonists or antagonists thereof described herein, which are shown to alter or impact endothelial cell function, proliferation, and/or form, are likely to play an important role in the etiology and pathogenesis of many or all of the disorders noted above, and as such can serve as therapeutic targets to augment or inhibit these processes or for vascular-related drug targeting in these disorders.

5.2.4.11. Administration Protocols, Schedules, Doses, and Formulations

The molecules herein and agonists and antagonists thereto are pharmaceutically useful as a prophylactic and therapeutic agent for various disorders and diseases as set forth above.

Therapeutic compositions of the PRO polypeptides or agonists or antagonists are prepared for storage by mixing the desired molecule having the appropriate degree of purity with optional pharmaceutically acceptable carriers, excipients, or stabilizers (Remington's Pharmaceutical Sciences, 16th edition, Osol, A. ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.*, Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

Additional examples of such carriers include ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts, or electrolytes such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, and polyethylene glycol. Carriers for topical or gel-based forms of agonist or antagonist include polysaccharides such as sodium carboxymethylcellulose or methylcellulose, polyvinylpyrrolidone, polyacrylates, polyoxyethylene-polyoxypropylene-block polymers, polyethylene glycol, and wood wax alcohols. For all administrations, conventional depot forms are suitably used. Such forms include, for example, microcapsules, nano-capsules, liposomes, plasters, inhalation forms, nose sprays, sublingual tablets, and sustained-release preparations. The PRO polypeptides or agonists or antagonists will typically be formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml.

Another formulation comprises incorporating a PRO polypeptide or agonist or antagonist thereof into formed articles. Such articles can be used in modulating endothelial cell growth and angiogenesis. In addition, tumor invasion and metastasis may be modulated with these articles.

PRO polypeptides or agonists or antagonists to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes, prior to or following lyophilization and reconstitution. PRO polypeptides ordinarily will be stored in lyophilized form or in solution if administered systemically. If in lyophilized form, the PRO polypeptide or agonist or antagonist thereto is typically formulated in combination with other ingredients for reconstitution with an appropriate diluent at the time for use. An example of a liquid formulation of a PRO polypeptide or agonist or antagonist is a sterile, clear, colorless unpreserved solution filled in a single-dose vial for subcutaneous injection. Preserved pharmaceutical compositions suitable for repeated use may contain, for example, depending mainly on the indication and type of polypeptide:

a) PRO polypeptide or agonist or antagonist thereto;
b) a buffer capable of maintaining the pH in a range of maximum stability of the polypeptide or other molecule in solution, preferably about 4-8;
c) a detergent/surfactant primarily to stabilize the polypeptide or molecule against agitation-induced aggregation;
d) an isotonifier;
e) a preservative selected from the group of phenol, benzyl alcohol and a benzethonium halide, *e.g.*, chloride; and
f) water.

If the detergent employed is non-ionic, it may, for example, be polysorbates (*e.g.*, POLYSORBATE™ (TWEEN™) 20, 80, etc.) or poloxamers (*e.g.*, POLOXAMER™ 188). The use of non-ionic surfactants permits the formulation to be exposed to shear surface stresses without causing denaturation of the polypeptide. Further, such surfactant-containing formulations may be employed in aerosol devices such as those used in a pulmonary dosing, and needleless jet injector guns (*see*, *e.g.*, EP 257,956).

An isotonifier may be present to ensure isotonicity of a liquid composition of the PRO polypeptide or agonist or antagonist thereto, and includes polyhydric sugar alcohols, preferably trihydric or higher sugar alcohols, such as glycerin, erythritol, arabitol, xylitol, sorbitol, and mannitol. These sugar alcohols can be used alone or in combination. Alternatively, sodium chloride or other appropriate inorganic salts may be used to render the solutions isotonic.

The buffer may, for example, be an acetate, citrate, succinate, or phosphate buffer depending on the pH desired. The pH of one type of liquid formulation of this invention is buffered in the range of about 4 to 8, preferably about physiological pH.

The preservatives phenol, benzyl alcohol and benzethonium halides, *e.g.*, chloride, are known antimicrobial agents that may be employed.

Therapeutic PRO polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle. The formulations are preferably administered as repeated intravenous (i.v.), subcutaneous (s.c.), or intramuscular (i.m.) injections, or as aerosol formulations suitable for intranasal or intrapulmonary delivery (for intrapulmonary delivery *see*, *e.g.*, EP 257,956).

PRO polypeptides can also be administered in the form of sustained-released preparations. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the protein, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (*e.g.*, poly(2-hydroxyethyl-methacrylate) as described by Langer *et al.*, J. Biomed. Mater. Res., 15: 167-277 (1981) and Langer, Chem. Tech., 12: 98-105 (1982) or poly(vinylalcohol)), polylactides (U.S. Patent No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman *et al.*, Biopolymers, 22: 547-556 (1983)), non-degradable ethylene-vinyl acetate (Langer *et al.*, *supra*), degradable lactic acid-glycolic acid copolymers such as the Lupron Depot™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid (EP 133,988).

While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated proteins remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for protein stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

Sustained-release PRO polypeptide compositions also include liposomally entrapped PRO polypeptides. Liposomes containing the PRO polypeptide are prepared by methods known *per se*: DE 3,218,121; Epstein *et al.*, Proc. Natl. Acad. Sci. USA, 82: 3688-3692 (1985); Hwang *et al.*, Proc. Natl. Acad. Sci. USA, 77: 4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese patent application 83-118008; U.S. Patent Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. % cholesterol, the selected proportion being adjusted for the optimal therapy.

The therapeutically effective dose of a PRO polypeptide or agonist or antagonist thereto will, of course, vary depending on such factors as the pathological condition to be treated (including prevention), the method of administration, the type of compound being used for treatment, any co-therapy involved, the patient's age, weight, general medical condition, medical history, etc., and its determination is well within the skill of a practicing physician. Accordingly, it will be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the maximal therapeutic effect. If the PRO polypeptide has a narrow host range, for the treatment of human patients formulations comprising human PRO polypeptide, more preferably native-sequence human PRO polypeptide, are preferred. The clinician will administer the PRO polypeptide until a dosage is reached that achieves the desired effect for treatment of the condition in question. For example, if the objective is the treatment of CHF, the amount would be one that inhibits the progressive cardiac hypertrophy associated with this condition. The progress of this therapy is easily monitored by echo cardiography. Similarly, in patients with hypertrophic cardiomyopathy, the PRO polypeptide can be administered on an empirical basis.

With the above guidelines, the effective dose generally is within the range of from about 0.001 to about 1.0 mg/kg, more preferably about 0.01-1.0 mg/kg, most preferably about 0.01-0.1 mg/kg.

For non-oral use in treating human adult hypertension, it is advantageous to administer the PRO polypeptide in the form of an injection at about 0.01 to 50 mg, preferably about 0.05 to 20 mg, most preferably 1 to 20 mg, per kg body weight, 1 to 3 times daily by intravenous injection. For oral administration, a molecule based on the PRO polypeptide is preferably administered at about 5 mg to 1 g, preferably about 10 to 100 mg, per kg body weight, 1 to 3 times daily. It should be appreciated that endotoxin contamination should be kept minimally at a safe level, for example, less than 0.5 ng/mg protein. Moreover, for human administration, the formulations preferably meet sterility, pyrogenicity, general safety, and purity as required by FDA Office and Biologics standards.

The dosage regimen of a pharmaceutical composition containing the PRO polypeptide to be used in tissue regeneration will be determined by the attending physician considering various factors that modify the action of the polypeptides, *e.g.*, amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (*e.g.*, bone), the patient's age, sex, and diet, the severity of any infection, time of administration, and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF-I, to the final composition may also affect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations, and tetracycline labeling.

The route of PRO polypeptide or antagonist or agonist administration is in accord with known methods, *e.g.*, by injection or infusion by intravenous, intramuscular, intracerebral, intraperitoneal, intracerobrospinal, subcutaneous, intraocular, intraarticular, intrasynovial, intrathecal, oral, topical, or inhalation routes, or by sustained-release systems as noted below. The PRO polypeptide or agonist or antagonists thereof also are suitably administered by intratumoral, peritumoral, intralesional, or perilesional routes, to exert local as well as systemic therapeutic effects. The intraperitoneal route is expected to be particularly useful, for example, in the treatment of ovarian tumors.

If a peptide or small molecule is employed as an antagonist or agonist, it is preferably administered orally or non-orally in the form of a liquid or solid to mammals.

Examples of pharmacologically acceptable salts of molecules that form salts and are useful hereunder include alkali metal salts (*e.g.*, sodium salt, potassium salt), alkaline earth metal salts (*e.g.*, calcium salt, magnesium salt), ammonium salts, organic base salts (*e.g.*, pyridine salt, triethylamine salt), inorganic acid salts (*e.g.*, hydrochloride, sulfate, nitrate), and salts of organic acid (*e.g.*, acetate, oxalate, p-toluenesulfonate).

For compositions herein that are useful for bone, cartilage, tendon, or ligament regeneration, the therapeutic method includes administering the composition topically, systemically, or locally as an implant or device. When administered, the therapeutic composition for use is in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage, or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Preferably, for bone and/or cartilage formation, the composition would include a matrix capable of delivering the

protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and preferably capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance, and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalcium phosphate, hydroxyapatite, polylactic acid, polyglycolic acid, and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxyapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above-mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalcium phosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

One specific embodiment is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the polypeptide compositions from disassociating from the matrix.

One suitable family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydoxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose, one preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer, and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt%, based on total formulation weight, which represents the amount necessary to prevent desorption of the polypeptide (or its antagonist) from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the polypeptide (or its antagonist) the opportunity to assist the osteogenic activity of the progenitor cells.

5.2.4.12. Combination Therapies

The effectiveness of the PRO polypeptide or an agonist or antagonist thereof in preventing or treating the disorder in question may be improved by administering the active agent serially or in combination with another agent that is effective for those purposes, either in the same composition or as separate compositions.

For example, for treatment of cardiac hypertrophy, PRO polypeptide therapy can be combined with the administration of inhibitors of known cardiac myocyte hypertrophy factors, *e.g.*, inhibitors of α-adrenergic agonists such as phenylephrine; endothelin-1 inhibitors such as BOSENTAN™ and MOXONODIN™; inhibitors to CT-1

(U.S. Pat. No. 5,679,545); inhibitors to LIF; ACE inhibitors; des-aspartate-angiotensin I inhibitors (U.S. Pat. No. 5,773,415), and angiotensin II inhibitors.

For treatment of cardiac hypertrophy associated with hypertension, the PRO polypeptide can be administered in combination with β-adrenergic receptor blocking agents, *e.g.*, propranolol, timolol, tertalolol, carteolol, nadolol, betaxolol, penbutolol, acetobutolol, atenolol, metoprolol, or carvedilol; ACE inhibitors, *e.g.*, quinapril, captopril, enalapril, ramipril, benazepril, fosinopril, or lisinopril; diuretics, *e.g.*, chlorothiazide, hydrochlorothiazide, hydroflumethazide, methylchlothiazide, benzthiazide, dichlorphenamide, acetazolamide, or indapamide; and/or calcium channel blockers, *e.g.*, diltiazem, nifedipine, verapamil, or nicardipine. Pharmaceutical compositions comprising the therapeutic agents identified herein by their generic names are commercially available, and are to be administered following the manufacturers' instructions for dosage, administration, adverse effects, contraindications, etc. *See*, *e.g.*, Physicians' Desk Reference (Medical Economics Data Production Co.: Montvale, N.J., 1997), 51th Edition.

Preferred candidates for combination therapy in the treatment of hypertrophic cardiomyopathy are β-adrenergic-blocking drugs (*e.g.*, propranolol, timolol, tertalolol, carteolol, nadolol, betaxolol, penbutolol, acetobutolol, atenolol, metoprolol, or carvedilol), verapamil, difedipine, or diltiazem. Treatment of hypertrophy associated with high blood pressure may require the use of antihypertensive drug therapy, using calcium channel blockers, *e.g.*, diltiazem, nifedipine, verapamil, or nicardipine; β-adrenergic blocking agents; diuretics, *e.g.*, chlorothiazide, hydrochlorothiazide, hydroflumethazide, methylchlothiazide, benzthiazide, dichlorphenamide, acetazolamide, or indapamide; and/or ACE-inhibitors, *e.g.*, quinapril, captopril, enalapril, ramipril, benazepril, fosinopril, or lisinopril.

For other indications, PRO polypeptides or their agonists or antagonists may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as EGF, PDGF, TGF-α or TGF-β, IGF, FGF, and CTGF.

In addition, PRO polypeptides or their agonists or antagonists used to treat cancer may be combined with cytotoxic, chemotherapeutic, or growth-inhibitory agents as identified above. Also, for cancer treatment, the PRO polypeptide or agonist or antagonist thereof is suitably administered serially or in combination with radiological treatments, whether involving irradiation or administration of radioactive substances.

The effective amounts of the therapeutic agents administered in combination with the PRO polypeptide or agonist or antagonist thereof will be at the physician's or veterinarian's discretion. Dosage administration and adjustment is done to achieve maximal management of the conditions to be treated. For example, for treating hypertension, these amounts ideally take into account use of diuretics or digitalis, and conditions such as hyper- or hypotension, renal impairment, etc. The dose will additionally depend on such factors as the type of the therapeutic agent to be used and the specific patient being treated. Typically, the amount employed will be the same dose as that used, if the given therapeutic agent is administered without the PRO polypeptide.

5.2.4.13. Articles of Manufacture

An article of manufacture such as a kit containing the PRO polypeptide or agonists or antagonists thereof useful for the diagnosis or treatment of the disorders described above comprises at least a container and a label. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition that is effective for diagnosing or treating the condition and may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The active agent in the composition is the PRO polypeptide or an agonist or antagonist thereto. The label on, or associated with, the container indicates that the composition is used for diagnosing or treating the condition of choice. The article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution, and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts with instructions for use. The article of manufacture may also comprise a second or third container with another active agent as described above.

5.2.5. Antibodies

Some of the most promising drug candidates according to the present invention are antibodies and antibody fragments that may inhibit the production or the gene product of the genes identified herein and/or reduce the activity of the gene products.

5.2.5.1. Polyclonal Antibodies

Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. The immunizing agent may include the PRO polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include, but are not limited to, keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants that may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A or synthetic trehalose dicorynomycolate). The immunization protocol may be selected by one skilled in the art without undue experimentation.

5.2.5.2. Monoclonal Antibodies

The anti-PRO antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler and Milstein, Nature, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal is typically immunized with an

immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

The immunizing agent will typically include the PRO polypeptide or a fusion protein thereof. Generally, either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell. Goding, Monoclonal Antibodies: Principles and Practice (New York: Academic Press, 1986), pp. 59-103. Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine, and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high-level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies. Kozbor, J. Immunol., 133:3001 (1984); Brodeur *et al.*, Monoclonal Antibody Production Techniques and Applications (Marcel Dekker, Inc.: New York, 1987) pp. 51-63.

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against the PRO polypeptide. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980).

After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods. Goding, *supra*. Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be grown *in vivo* as ascites in a mammal.

The monoclonal antibodies secreted by the subclones may be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the

invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy- and light-chain constant domains in place of the homologous murine sequences (U.S. Patent No. 4,816,567; Morrison *et al.*, *supra*) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy chain. The heavy chain is truncated generally at any point in the Fc region so as to prevent heavy-chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

In vitro methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly Fab fragments, can be accomplished using routine techniques known in the art.

5.2.5.3. Human and Humanized Antibodies

The anti-PRO antibodies may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (*e.g.*, murine) antibodies are chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequences of antibodies) that contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a CDR of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin, and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody preferably also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. Jones *et al.*, Nature, 321: 522-525 (1986); Riechmann *et al.*, Nature, 332: 323-329 (1988); Presta, Curr. Op. Struct. Biol., 2:593-596 (1992).

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source that is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers (Jones *et al.*, Nature, 321: 522-525 (1986); Riechmann *et al.*, Nature, 332: 323-327 (1988); Verhoeyen *et al.*, Science, 239: 1534-

1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

Human antibodies can also be produced using various techniques known in the art, including phage display libraries. Hoogenboom and Winter, J. Mol. Biol., 227: 381 (1991); Marks *et al.*, J. Mol. Biol., 222: 581 (1991). The techniques of Cole *et al.* and Boerner *et al.* are also available for the preparation of human monoclonal antibodies. Cole *et al.*, Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985) and Boerner *et al.*, J. Immunol., 147(1): 86-95 (1991). Similarly, human antibodies can be made by introducing human immunoglobulin loci into transgenic animals, *e.g.*, mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed that closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016, and in the following scientific publications: Marks *et al.*, Bio/Technology, 10: 779-783 (1992); Lonberg *et al.*, Nature, 368: 856-859 (1994); Morrison, Nature, 368: 812-813 (1994); Fishwild *et al.*, Nature Biotechnology, 14: 845-851 (1996); Neuberger, Nature Biotechnology, 14: 826 (1996); Lonberg and Huszar, Intern. Rev. Immunol., 13: 65-93 (1995).

5.2.5.4. Bispecific Antibodies

Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for the PRO polypeptide, the other one is for any other antigen, and preferably for a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin heavy-chain/light-chain pairs, where the two heavy chains have different specificities. Milstein and Cuello, Nature, 305: 537-539 (1983). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in Traunecker *et al.*, EMBO J., 10: 3655-3659 (1991).

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant-domain sequences. The fusion preferably is with an immunoglobulin heavy-chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. For further

details of generating bispecific antibodies, *see*, for example, Suresh *et al.*, Methods in Enzymology, 121: 210 (1986).

5.2.5.5. Heteroconjugate Antibodies

Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune-system cells to unwanted cells (U.S. Patent No. 4,676,980), and for treatment of HIV infection. WO 91/00360; WO 92/200373; EP 03089. It is contemplated that the antibodies may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide-exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

5.2.5.6. Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, *e.g.*, the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) may be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). *See*, Caron *et al.*, J. Exp. Med., 176: 1191-1195 (1992) and Shopes, J. Immunol., 148: 2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff *et al.*, Cancer Research, 53: 2560-2565 (1993). Alternatively, an antibody can be engineered that has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. *See*, Stevenson *et al.*, Anti-Cancer Drug Design, 3: 219-230 (1989).

5.2.5.7. Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (*e.g.*, an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (*i.e.*, a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ^{212}Bi, ^{131}I, ^{131}In, ^{90}Y, and ^{186}Re.

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives

of imidoesters (such as dimethyl adipimidate HCl), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, Science, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. *See*, WO94/11026.

In another embodiment, the antibody may be conjugated to a "receptor" (such as streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (*e.g.*, avidin) that is conjugated to a cytotoxic agent (*e.g.*, a radionucleotide).

5.2.5.8. Immunoliposomes

The antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein *et al.*, Proc. Natl. Acad. Sci. USA, 82: 3688 (1985); Hwang *et al.*, Proc. Natl. Acad. Sci. USA, 77: 4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556.

Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin *et al.*, J. Biol. Chem., 257: 286-288 (1982) via a disulfide-interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. *See*, Gabizon *et al.*, J. National Cancer Inst., 81(19): 1484 (1989).

5.2.5.9. Pharmaceutical Compositions of Antibodies

Antibodies specifically binding a PRO polypeptide identified herein, as well as other molecules identified by the screening assays disclosed hereinbefore, can be administered for the treatment of various disorders as noted above and below in the form of pharmaceutical compositions.

If the PRO polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also be used to deliver the antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. *See, e.g.*, Marasco *et al.*, Proc. Natl. Acad. Sci. USA, 90: 7889-7893 (1993).

The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, *supra*.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.*, films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT ™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

5.2.5.10. Methods of Treatment using the Antibody

It is contemplated that the antibodies to a PRO polypeptide may be used to treat various cardiovascular, endothelial, and angiogenic conditions as noted above.

The antibodies are administered to a mammal, preferably a human, in accord with known methods, such as intravenous administration as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerobrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes. Intravenous administration of the antibody is preferred.

Other therapeutic regimens may be combined with the administration of the antibodies of the instant invention as noted above. For example, if the antibodies are to treat cancer, the patient to be treated with such

antibodies may also receive radiation therapy. Alternatively, or in addition, a chemotherapeutic agent may be administered to the patient. Preparation and dosing schedules for such chemotherapeutic agents may be used according to manufacturers' instructions or as determined empirically by the skilled practitioner. Preparation and dosing schedules for such chemotherapy are also described in Chemotherapy Service, Ed., M.C. Perry (Williams & Wilkins: Baltimore, MD, 1992). The chemotherapeutic agent may precede, or follow administration of the antibody, or may be given simultaneously therewith. The antibody may be combined with an anti-estrogen compound such as tamoxifen or EVISTA™ or an anti-progesterone such as onapristone (*see*, EP 616812) in dosages known for such molecules.

If the antibodies are used for treating cancer, it may be desirable also to administer antibodies against other tumor-associated antigens, such as antibodies that bind to one or more of the ErbB2, EGFR, ErbB3, ErbB4, or VEGF receptor(s). These also include the agents set forth above. Also, the antibody is suitably administered serially or in combination with radiological treatments, whether involving irradiation or administration of radioactive substances. Alternatively, or in addition, two or more antibodies binding the same or two or more different antigens disclosed herein may be co-administered to the patient. Sometimes, it may be beneficial also to administer one or more cytokines to the patient. In a preferred embodiment, the antibodies herein are co-administered with a growth-inhibitory agent. For example, the growth-inhibitory agent may be administered first, followed by an antibody of the present invention. However, simultaneous administration or administration of the antibody of the present invention first is also contemplated. Suitable dosages for the growth-inhibitory agent are those presently used and may be lowered due to the combined action (synergy) of the growth-inhibitory agent and the antibody herein.

In one embodiment, vascularization of tumors is attacked in combination therapy. The anti-PRO polypeptide antibody and another antibody (*e.g.*, anti-VEGF) are administered to tumor-bearing patients at therapeutically effective doses as determined, for example, by observing necrosis of the tumor or its metastatic foci, if any. This therapy is continued until such time as no further beneficial effect is observed or clinical examination shows no trace of the tumor or any metastatic foci. Then TNF is administered, alone or in combination with an auxiliary agent such as alpha-, beta-, or gamma-interferon, anti-HER2 antibody, heregulin, anti-heregulin antibody, D-factor, interleukin-1 (IL-1), interleukin-2 (IL-2), granulocyte-macrophage colony stimulating factor (GM-CSF), or agents that promote microvascular coagulation in tumors, such as anti-protein C antibody, anti-protein S antibody, or C4b binding protein (*see*, WO 91/01753, published 21 February 1991), or heat or radiation.

Since the auxiliary agents will vary in their effectiveness, it is desirable to compare their impact on the tumor by matrix screening in conventional fashion. The administration of anti-PRO polypeptide antibody and TNF is repeated until the desired clinical effect is achieved. Alternatively, the anti-PRO polypeptide antibody is administered together with TNF and, optionally, auxiliary agent(s). In instances where solid tumors are found in the limbs or in other locations susceptible to isolation from the general circulation, the therapeutic agents described herein are administered to the isolated tumor or organ. In other embodiments, a FGF or PDGF antagonist, such as an anti-FGF or an anti-PDGF neutralizing antibody, is administered to the patient in conjunction with the anti-PRO

polypeptide antibody. Treatment with anti-PRO polypeptide antibodies preferably may be suspended during periods of wound healing or desirable neovascularization.

For the prevention or treatment of cardiovascular, endothelial, and angiogenic disorder, the appropriate dosage of an antibody herein will depend on the type of disorder to be treated, as defined above, the severity and course of the disease, whether the antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, and the discretion of the attending physician. The antibody is suitably administered to the patient at one time or over a series of treatments.

For example, depending on the type and severity of the disorder, about 1 μg/kg to 50 mg/kg (*e.g.*, 0.1-20 mg/kg) of antibody is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. A typical daily or weekly dosage might range from about 1 μg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is repeated or sustained until a desired suppression of disorder symptoms occurs. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays, including, for example, radiographic tumor imaging.

5.2.5.11. <u>Articles of Manufacture with Antibodies</u>

An article of manufacture containing a container with the antibody and a label is also provided. Such articles are described above, wherein the active agent is an anti-PRO antibody.

5.2.5.12. <u>Diagnosis and Prognosis of Tumors using Antibodies</u>

If the indication for which the antibodies are used is cancer, while cell-surface proteins, such as growth receptors over expressed in certain tumors, are excellent targets for drug candidates or tumor (*e.g.*, cancer) treatment, the same proteins along with PRO polypeptides find additional use in the diagnosis and prognosis of tumors. For example, antibodies directed against the PRO polypeptides may be used as tumor diagnostics or prognostics.

For example, antibodies, including antibody fragments, can be used qualitatively or quantitatively to detect the expression of genes including the gene encoding the PRO polypeptide. The antibody preferably is equipped with a detectable, *e.g.*, fluorescent label, and binding can be monitored by light microscopy, flow cytometry, fluorimetry, or other techniques known in the art. Such binding assays are performed essentially as described above.

In situ detection of antibody binding to the marker gene products can be performed, for example, by immunofluorescence or immunoelectron microscopy. For this purpose, a histological specimen is removed from the patient, and a labeled antibody is applied to it, preferably by overlaying the antibody on a biological sample. This procedure also allows for determining the distribution of the marker gene product in the tissue examined. It will be apparent to those skilled in the art that a wide variety of histological methods are readily available for *in situ* detection.

The following Examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

The disclosures of all patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

6. EXAMPLES

Commercially available reagents referred to in the Examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following Examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA. Unless otherwise noted, the present invention uses standard procedures of recombinant DNA technology, such as those described hereinabove and in the following textbooks: Sambrook *et al., supra*; Ausubel *et al.,* Current Protocols in Molecular Biology (Green Publishing Associates and Wiley Interscience, N.Y., 1989); Innis *et al.,* PCR Protocols: A Guide to Methods and Applications (Academic Press, Inc.: N.Y., 1990); Harlow *et al.,* Antibodies: A Laboratory Manual (Cold Spring Harbor Press: Cold Spring Harbor, 1988); Gait, Oligonucleotide Synthesis (IRL Press: Oxford, 1984); Freshney, Animal Cell Culture, 1987; Coligan *et al.,* Current Protocols in Immunology, 1991.

6.1. EXAMPLE 1: Extracellular Domain Homology Screening to Identify Novel Polypeptides and cDNA Encoding Therefor

The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included public databases (*e.g.*, Dayhoff, GenBank), and proprietary databases (*e.g.* LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST-2 (Altschul *et al.*, Methods in Enzymology, 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons with a BLAST score of 70 (or in some cases, 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, WA).

Using this extracellular domain homology screen, consensus DNA sequences were assembled relative to the other identified EST sequences using phrap. In addition, the consensus DNA sequences obtained were often (but not always) extended using repeated cycles of BLAST or BLAST-2 and phrap to extend the consensus sequence as far as possible using the sources of EST sequences discussed above.

Based upon the consensus sequences obtained as described above, oligonucleotides were then synthesized and used to identify by PCR a cDNA library that contained the sequence of interest and for use as probes to isolate a clone of the full-length coding sequence for a PRO polypeptide. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about 1-1.5 kbp. In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel *et al.*, Current Protocols in Molecular

Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI hemikinased adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or pRKD; pRK5B is a precursor of pRK5D that does not contain the SfiI site; *see*, Holmes *et al.*, Science, 253:1278-1280 (1991)) in the unique XhoI and NotI sites.

6.2. EXAMPLE 2: Isolation of cDNA Clones by Amylase Screening

6.2.1. Preparation of oligo dT primed cDNA library

mRNA was isolated from a human tissue of interest using reagents and protocols from Invitrogen, San Diego, CA (Fast Track 2). This RNA was used to generate an oligo dT primed cDNA library in the vector pRK5D using reagents and protocols from Life Technologies, Gaithersburg, MD (Super Script Plasmid System). In this procedure, the double stranded cDNA was sized to greater than 1000 bp and the SalI/NotI linkered cDNA was cloned into XhoI/NotI cleaved vector. pRK5D is a cloning vector that has an sp6 transcription initiation site followed by an SfiI restriction enzyme site preceding the XhoI/NotI cDNA cloning sites.

6.2.2. Preparation of random primed cDNA library

A secondary cDNA library was generated in order to preferentially represent the 5' ends of the primary cDNA clones. Sp6 RNA was generated from the primary library (described above), and this RNA was used to generate a random primed cDNA library in the vector pSST-AMY.0 using reagents and protocols from Life Technologies (Super Script Plasmid System, referenced above). In this procedure the double stranded cDNA was sized to 500-1000 bp, linkered with blunt to NotI adaptors, cleaved with SfiI, and cloned into SfiI/NotI cleaved vector. pSST-AMY.0 is a cloning vector that has a yeast alcohol dehydrogenase promoter preceding the cDNA cloning sites and the mouse amylase sequence (the mature sequence without the secretion signal) followed by the yeast alcohol dehydrogenase terminator, after the cloning sites. Thus, cDNAs cloned into this vector that are fused in frame with amylase sequence will lead to the secretion of amylase from appropriately transfected yeast colonies.

6.2.3. Transformation and Detection

DNA from the library described in paragraph 2 above was chilled on ice to which was added electrocompetent DH10B bacteria (Life Technologies, 20 ml). The bacteria and vector mixture was then electroporated as recommended by the manufacturer. Subsequently, SOC media (Life Technologies, 1 ml) was added and the mixture was incubated at 37°C for 30 minutes. The transformants were then plated onto 20 standard 150 mm LB plates containing ampicillin and incubated for 16 hours (37°C). Positive colonies were scraped off the plates and the DNA was isolated from the bacterial pellet using standard protocols, *e.g.*, CsCl-gradient. The purified DNA was then carried on to the yeast protocols below.

The yeast methods were divided into three categories: (1) Transformation of yeast with the plasmid/cDNA combined vector; (2) Detection and isolation of yeast clones secreting amylase; and (3) PCR amplification of the insert directly from the yeast colony and purification of the DNA for sequencing and further analysis.

The yeast strain used was HD56-5A (ATCC-90785). This strain has the following genotype: MAT alpha, ura3-52, leu2-3, leu2-112, his3-11, his3-15, MAL^+, SUC^+, GAL^+. Preferably, yeast mutants can be employed that have deficient post-translational pathways. Such mutants may have translocation deficient alleles in *sec*71, *sec*72, *sec*62, with truncated *sec*71 being most preferred. Alternatively, antagonists (including antisense nucleotides and/or ligands) which interfere with the normal operation of these genes, other proteins implicated in this post translation pathway (*e.g.*, SEC61p, SEC72p, SEC62p, SEC63p, TDJ1p or SSA1p-4p) or the complex formation of these proteins may also be preferably employed in combination with the amylase-expressing yeast.

Transformation was performed based on the protocol outlined by Gietz *et al.*, Nucl. Acid. Res., 20:1425 (1992). Transformed cells were then inoculated from agar into YEPD complex media broth (100 ml) and grown overnight at 30°C. The YEPD broth was prepared as described in Kaiser *et al.*, Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 207 (1994). The overnight culture was then diluted to about 2 x 10^6 cells/ml (approx. OD_{600}=0.1) into fresh YEPD broth (500 ml) and regrown to 1 x 10^7 cells/ml (approx. OD_{600}=0.4-0.5).

The cells were then harvested and prepared for transformation by transfer into GS3 rotor bottles in a Sorval GS3 rotor at 5,000 rpm for 5 minutes, the supernatant discarded, and then resuspended into sterile water, and centrifuged again in 50 ml falcon tubes at 3,500 rpm in a Beckman GS-6KR centrifuge. The supernatant was discarded and the cells were subsequently washed with LiAc/TE (10 ml, 10 mM Tris-HCl, 1 mM EDTA pH 7.5, 100 mM Li_2OOCCH_3), and resuspended into LiAc/TE (2.5 ml).

Transformation took place by mixing the prepared cells (100 µl) with freshly denatured single stranded salmon testes DNA (Lofstrand Labs, Gaithersburg, MD) and transforming DNA (1 µg, vol. < 10 µl) in microfuge tubes. The mixture was mixed briefly by vortexing, then 40% PEG/TE (600 µl, 40% polyethylene glycol-4000, 10 mM Tris-HCl, 1 mM EDTA, 100 mM Li_2OOCCH_3, pH 7.5) was added. This mixture was gently mixed and incubated at 30°C while agitating for 30 minutes. The cells were then heat shocked at 42°C for 15 minutes, and the reaction vessel centrifuged in a microfuge at 12,000 rpm for 5-10 seconds, decanted and resuspended into TE (500 µl, 10 mM Tris-HCl, 1 mM EDTA pH 7.5) followed by recentrifugation. The cells were then diluted into TE (1 ml) and aliquots (200 µl) were spread onto the selective media previously prepared in 150 mm growth plates (VWR).

Alternatively, instead of multiple small reactions, the transformation was performed using a single, large scale reaction, wherein reagent amounts were scaled up accordingly.

The selective media used was a synthetic complete dextrose agar lacking uracil (SCD-Ura) prepared as described in Kaiser *et al.*, Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 208-210 (1994). Transformants were grown at 30°C for 2-3 days.

The detection of colonies secreting amylase was performed by including red starch in the selective growth media. Starch was coupled to the red dye (Reactive Red-120, Sigma) as per the procedure described by Biely *et*

al., Anal. Biochem., 172:176-179 (1988). The coupled starch was incorporated into the SCD-Ura agar plates at a final concentration of 0.15% (w/v), and was buffered with potassium phosphate to a pH of 7.0 (50-100 mM final concentration).

The positive colonies were picked and streaked across fresh selective media (onto 150 mm plates) in order to obtain well isolated and identifiable single colonies. Well isolated single colonies positive for amylase secretion were detected by direct incorporation of red starch into buffered SCD-Ura agar. Positive colonies were determined by their ability to break down starch resulting in a clear halo around the positive colony visualized directly.

6.2.4. Isolation of DNA by PCR Amplification

When a positive colony was isolated, a portion of it was picked by a toothpick and diluted into sterile water (30 µl) in a 96 well plate. At this time, the positive colonies were either frozen and stored for subsequent analysis or immediately amplified. An aliquot of cells (5 µl) was used as a template for the PCR reaction in a 25 µl volume containing: 0.5 µl Klentaq (Clontech, Palo Alto, CA); 4.0 µl 10 mM dNTP's (Perkin Elmer-Cetus); 2.5 µl Kentaq buffer (Clontech); 0.25 µl forward oligo 1; 0.25 µl reverse oligo 2; 12.5 µl distilled water. The sequence of the forward oligonucleotide 1 was:

5'-TGTAAAACGACGGCCAGTTAAATAGACCTGCAATTATTAATCT-3' (SEQ ID NO:382)

The sequence of reverse oligonucleotide 2 was:

5'-CAGGAAACAGCTATGACCACCTGCACACCTGCAAATCCATT-3' (SEQ ID NO:383)

PCR was then performed as follows:

a.		Denature	92°C,	5 minutes
b.	3 cycles of:	Denature	92°C,	30 seconds
		Anneal	59°C,	30 seconds
		Extend	72°C,	60 seconds
c.	3 cycles of:	Denature	92°C,	30 seconds
		Anneal	57°C,	30 seconds
		Extend	72°C,	60 seconds
d.	25 cycles of:	Denature	92°C,	30 seconds
		Anneal	55°C,	30 seconds
		Extend	72°C,	60 seconds
e.		Hold	4°C	

The underlined regions of the oligonucleotides annealed to the ADH promoter region and the amylase region, respectively, and amplified a 307 bp region from vector pSST-AMY.0 when no insert was present. Typically, the first 18 nucleotides of the 5' end of these oligonucleotides contained annealing sites for the sequencing primers. Thus, the total product of the PCR reaction from an empty vector was 343 bp. However, signal sequence-fused cDNA resulted in considerably longer nucleotide sequences.

Following the PCR, an aliquot of the reaction (5 μl) was examined by agarose gel electrophoresis in a 1% agarose gel using a Tris-Borate-EDTA (TBE) buffering system as described by Sambrook *et al., supra*. Clones resulting in a single strong PCR product larger than 400 bp were further analyzed by DNA sequencing after purification with a 96 Qiaquick PCR clean-up column (Qiagen Inc., Chatsworth, CA).

6.3. EXAMPLE 3: Isolation of cDNA Clones Using Signal Algorithm Analysis

Various polypeptide-encoding nucleic acid sequences were identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc., (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (*e.g.*, GenBank) and/or private (LIFESEQ®, Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon(s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals. Use of this algorithm resulted in the identification of numerous polypeptide-encoding nucleic acid sequences.

6.4. EXAMPLE 4: Isolation of cDNA clones Encoding Human PRO Polypeptides

Using the techniques described in Examples 1 to 3 above, numerous full-length cDNA clones were identified as encoding PRO polypeptides as disclosed herein. These cDNAs were then deposited under the terms of the Budapest Treaty with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, USA (ATCC) as shown in Table 7 below.

Table 7

Material	ATCC Dep. No.	Deposit Date
23330-1390	209775	4/14/1998
23339-1130	209282	9/18/1997
26846-1397	203406	10/27/1998
26847-1395	209772	4/14/1998
27865-1091	209296	9/23/1997
30868-1156	1437-PTA	3/2/2000
30871-1157	209380	10/16/1997
32286-1191	209385	10/16/1997
33089-1132	209262	9/16/1997
33092-1202	209420	10/28/1997

33100-1159	209377	10/16/1997
33223-1136	209264	9/16/1997
34392-1170	209526	12/10/1997
34431-1177	209399	10/17/1997
34433-1308	209719	3/31/1998
34434-1139	209252	9/16/1997
35600-1162	209370	10/16/1997
35673-1201	209418	10/28/1997
35880-1160	209379	10/16/1997
35918-1174	209402	10/17/1997
36350-1158	209378	10/16/1997
36638-1056	209456	11/12/1997
38268-1188	209421	10/28/1997
40370-1217	209485	11/21/1997
40628-1216	209432	11/7/1997
43316-1237	209487	11/21/1997
44196-1353	209847	5/6/1998
45409-2511	203579	1/12/1999
45419-1252	209616	2/5/1998
46777-1253	209619	2/5/1998
48336-1309	209669	3/11/1998
48606-1479	203040	7/1/1998
49435-1219	209480	11/21/1997
49631-1328	209806	4/28/1998
50919-1361	209848	5/6/1998
50920-1325	209700	3/26/1998
50921-1458	209859	5/12/1998
52758-1399	209773	4/14/1998
53517-1366-1	209802	4/23/1998
53915-1258	209593	1/21/1998
53974-1401	209774	4/14/1998
53987-1438	209858	5/12/1998
56047-1456	209948	6/9/1998
56050-1455	203011	6/23/1998
56110-1437	203113	8/11/1998
56405-1357	209849	5/6/1998
56433-1406	209857	5/12/1998

56439-1376	209864	5/14/1998
56529-1647	203293	9/29/1998
56865-1491	203022	6/23/1998
56965-1356	209842	5/6/1998
57033-1403-1	209905	5/27/1998
57037-1444	209903	5/27/1998
57039-1402	209777	4/14/1998
57689-1385	209869	5/14/1998
57690-1374	209950	6/9/1998
57694-1341	203017	6/23/1998
57695-1340	203006	6/23/1998
57699-1412	203020	6/23/1998
57700-1408	203583	1/12/1999
57708-1411	203021	6/23/1998
57838-1337	203014	6/23/1998
58847-1383	209879	5/20/1998
58852-1637	203271	9/22/1998
58853-1423	203016	6/23/1998
59212-1627	203245	9/9/1998
59220-1514	209962	6/9/1998
59493-1420	203050	7/1/1998
59497-1496	209941	6/4/1998
59586-1520	203288	9/29/1998
59588-1571	203106	8/11/1998
59620-1463	209989	6/16/1998
59622-1334	209984	6/16/1998
59777-1480	203111	8/11/1998
59848-1512	203088	8/4/1998
59849-1504	209986	6/16/1998
60621-1516	203091	8/4/1998
60622-1525	203090	8/4/1998
60764-1533	203452	11/10/1998
60783-1611	203130	8/18/1998
61755-1554	203112	8/11/1998
62306-1570	203254	9/9/1998
62312-2558	203836	3/9/1999
62814-1521	203093	8/4/1998

62872-1509	203100	8/4/1998
64883-1526	203253	9/9/1998
64886-1601	203241	9/9/1998
64889-1541	203250	9/9/1998
64896-1539	203238	9/9/1998
64897-1628	203216	9/15/1998
64903-1553	203223	9/15/1998
64908-1163-1	203243	9/9/1998
64950-1590	203224	9/15/1998
65402-1540	203252	9/9/1998
65404-1551	203244	9/9/1998
65405-1547	203476	11/17/1998
65410-1569	203231	9/15/1998
65412-1523	203094	8/4/1998
66307-2661	431-PTA	7/27/1999
66526-1616	203246	9/9/1998
66659-1593	203269	9/22/1998
66660-1585	203279	9/22/1998
66667-1596	203267	9/22/1998
66672-1586	203265	9/22/1998
66675-1587	203282	9/22/1998
67300-1605	203163	8/25/1998
68818-2536	203657	2/9/1999
68862-2546	203652	2/9/1999
68872-1620	203160	8/25/1998
71290-1630	203275	9/22/1998
73736-1657	203466	11/17/1998
73739-1645	203270	9/22/1998
73742-1662	203316	10/6/1998
76385-1692	203664	2/9/1999
76393-1664	203323	10/6/1998
76399-1700	203472	11/17/1998
76400-2528	203573	1/12/1999
76510-2504	203477	11/17/1998
76529-1666	203315	10/6/1998
76532-1702	203473	11/17/1998
76541-1675	203409	10/27/1998

77503-1686	203362	10/20/1998
77624-2515	203553	12/22/1998
79230-2525	203549	12/22/1998
79862-2522	203550	12/22/1998
80145-2594	204-PTA	6/8/1999
80899-2501	203539	12/15/1998
81754-2532	203542	12/15/1998
81757-2512	203543	12/15/1998
81761-2583	203862	3/23/1999
82358-2738	510-PTA	8/10/1999
82364-2538	203603	1/20/1999
82403-2959	2317-PTA	8/1/2000
83500-2506	203391	10/29/1998
83560-2569	203816	3/2/1999
84210-2576	203818	3/2/1999
84920-2614	203966	4/27/1999
86576-2595	203868	3/23/1999
92218-2554	203834	3/9/1999
92233-2599	134-PTA	5/25/1999
92256-2596	203891	3/30/1999
92265-2669	256-PTA	6/22/1999
92274-2617	203971	4/27/1999
92929-2534-1	203586	1/12/1999
93011-2637	20-PTA	5/4/1999
94854-2586	203864	3/23/1999
96787-2534-1	203589	1/12/1999
96867-2620	203972	4/27/1999
96872-2674	550-PTA	8/17/1999
96878-2626	23-PTA	5/4/1999
96889-2641	119-PTA	5/25/1999
100312-2645	44-PTA	5/11/1999
105782-2693	387-PTA	7/20/1999
105849-2704	473-PTA	8/3/1999
108725-2766	863-PTA	10/19/1999
108769-2765	861-PTA	10/19/1999
119498-2965	2298-PTA	7/25/2000
119535-2756	613-PTA	8/31/1999

125185-2806	1031-PTA	12/7/1999
131639-2874	1784-PTA	4/25/2000
139623-2893	1670-PTA	4/11/2000
143076-2787	1028-PTA	12/7/1999
143276-2975	2387-PTA	8/8/2000
164625-2890	1535-PTA	3/21/2000
167678-2963	2302-PTA	7/25/2000
170021-2923	1906-PTA	5/23/2000
170212-3000	2583-PTA	10/10/2000
177313-2982	2251-PTA	7/19/2000

These deposits were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The deposits will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 USC § 122 and the Commissioner's rules pursuant thereto (including 37 CFR § 1.14 with particular reference to 886 OG 638).

The assignee of the present application has agreed that if a culture of the materials on deposit should die or be lost or destroyed when cultivated under suitable conditions, the materials will be promptly replaced on notification with another of the same. Availability of the deposited material is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

6.5 EXAMPLE 5: Isolation of cDNA clones Encoding Human PRO1873, PRO7223, PRO7248, PRO730, PRO532, PRO7261, PRO734, PRO771, PRO2010, PRO5723, PRO3444, PRO9940, PRO3562, PRO10008, PRO5730, PRO6008, PRO4527, PRO4538 and PRO4553

DNA molecules encoding the PRO1873, PRO7223, PRO7248, PRO730, PRO532, PRO7261, PRO734, PRO771, PRO2010, PRO5723, PRO3444, PRO9940, PRO3562, PRO10008, PRO5730, PRO6008, PRO4527, PRO4538 and PRO4553 polypeptides shown in the accompanying figures were obtained through GenBank.

6.6. EXAMPLE 6: Use of PRO as a Hybridization Probe

The following method describes use of a nucleotide sequence encoding PRO as a hybridization probe.

DNA comprising the coding sequence of full-length or mature PRO (as shown in accompanying figures) or a fragment thereof is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO) in human tissue cDNA libraries or human tissue genomic libraries.

Hybridization and washing of filters containing either library DNAs is performed under the following high-stringency conditions. Hybridization of radiolabeled probe derived from the gene encoding PRO polypeptide to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing of the filters is performed in an aqueous solution of 0.1x SSC and 0.1% SDS at 42°C.

DNAs having a desired sequence identity with the DNA encoding full-length native sequence can then be identified using standard techniques known in the art.

6.7. <u>EXAMPLE 7:</u> <u>Expression of PRO in *E. coli*</u>

This example illustrates preparation of an unglycosylated form of PRO by recombinant expression in *E. coli.*

The DNA sequence encoding PRO is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from *E. coli*; *see,* Bolivar *et al.*, <u>Gene,</u> <u>2</u>:95 (1977)) which contains genes for ampicillin and tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode for an antibiotic resistance gene, a trp promoter, a poly-His leader (including the first six STII codons, poly-His sequence, and enterokinase cleavage site), the PRO coding region, lambda transcriptional terminator, and an argU gene.

The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook *et al., supra.* Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized PRO protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

PRO may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding PRO is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an

expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110 fuhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an OD_{600} of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g $(NH_4)_2SO_4$, 0.71 g sodium citrate•$2H_2O$, 1.07 g KCl, 5.36 g Difco yeast extract, 5.36 g Sheffield hycase SF in 500 ml water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM $MgSO_4$) and grown for approximately 20-30 hours at 30°C with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

E. coli paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni^{2+}-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A_{280} absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

Fractions containing the desired folded PRO polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

Many of the PRO polypeptides disclosed herein were successfully expressed as descibed above.

6.8. EXAMPLE 8: Expression of PRO in mammalian cells

This example illustrates preparation of a potentially glycosylated form of PRO by recombinant expression in mammalian cells.

The vector, pRK5 (*see* EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the PRO DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the PRO DNA using ligation methods such as described in Sambrook *et al., supra*. The resulting vector is called pRK5-PRO.

In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 μg pRK5-PRO DNA is mixed with about 1 μg DNA encoding the VA RNA gene [Thimmappaya *et al.*, Cell, 31:543 (1982)] and dissolved in 500 μl of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M $CaCl_2$. To this mixture is added, dropwise, 500 μl of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM $NaPO_4$, and a precipitate is allowed to form for 10 minutes at 25°C. The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 μCi/ml ^{35}S-cysteine and 200 μCi/ml ^{35}S-methionine. After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of the PRO polypeptide. The cultures containing transfected cells may undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

In an alternative technique, PRO may be introduced into 293 cells transiently using the dextran sulfate method described by Somparyrac *et al.*, Proc. Natl. Acad. Sci., 12:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700 μg pRK5-PRO DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5 μg/ml bovine insulin and 0.1 μg/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed PRO can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

In another embodiment, PRO can be expressed in CHO cells. The pRK5-PRO can be transfected into CHO cells using known reagents such as $CaPO_4$ or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as ^{35}S-methionine. After determining the presence of a PRO polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested.

The medium containing the expressed PRO polypeptide can then be concentrated and purified by any selected method.

Epitope-tagged PRO may also be expressed in host CHO cells. The PRO may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-His tag into a Baculovirus expression vector. The poly-His tagged PRO insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 driven vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged PRO can then be concentrated and purified by any selected method, such as by Ni^{2+}-chelate affinity chromatography.

PRO may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (*e.g.*, extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or as a poly-His tagged form.

Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel *et al.*, Current Protocols of Molecular Biology, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used in expression in CHO cells is as described in Lucas *et al.*, Nucl. Acids Res., 24:9 (1774-1779 (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect® (Qiagen), Dosper® or Fugene® (Boehringer Mannheim). The cells are grown as described in Lucas *et al.*, *supra*. Approximately 3 x 10^7 cells are frozen in an ampule for further growth and production as described below.

The ampules containing the plasmid DNA are thawed by placement into a water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 ml of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 ml of selective media (0.2 μm filtered PS20 with 5% 0.2 μm diafiltered fetal bovine serum). The cells are then aliquoted into a 100 ml spinner containing 90 ml of selective media. After 1-2 days, the cells are transferred into a 250 ml spinner filled with 150 ml selective growth medium and incubated at 37°C. After another 2-3 days, 250 ml, 500 ml and 2000 ml spinners are seeded with 3 x 10^5 cells/ml. The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at 1.2 x 10^6 cells/ml. On day 0, the cell number and pH is determined. On day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 ml of 500 g/L

glucose and 0.6 ml of 10% antifoam (*e.g.*, 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability drops below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22 μm filter. The filtrate is either stored at 4°C or immediately loaded onto columns for purification.

For the poly-His tagged constructs, the proteins are purified using a Ni^{2+}-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni^{2+}-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows. The conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which has been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 μl of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

Many of the PRO polypeptides disclosed herein were successfully expressed as descibed above.

6.9. <u>EXAMPLE 9:</u> <u>Expression of PRO in Yeast</u>

The following method describes recombinant expression of PRO in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of PRO from the ADH2/GAPDH promoter. DNA encoding PRO and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of PRO. For secretion, DNA encoding PRO can be cloned into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native PRO signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of PRO.

Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant PRO can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing PRO may further be purified using selected column chromatography resins.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

6.10. EXAMPLE 10: Expression of PRO in Baculovirus-Infected Insect Cells

The following method describes recombinant expression in Baculovirus-infected insect cells.

The sequence coding for PRO is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-His tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding PRO or the desired portion of the coding sequence of PRO (such as the sequence encoding the extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular) is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfecting the above plasmid and BaculoGold™ virus DNA (Pharmingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley *et al.*, Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

Expressed poly-His tagged PRO can then be purified, for example, by Ni^{2+}-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert *et al.*, Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 ml Hepes, pH 7.9; 12.5 mM $MgCl_2$; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 µm filter. A Ni^{2+}-NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 ml, washed with 25 ml of water and equilibrated with 25 ml of loading buffer. The filtered cell extract is loaded onto the column at 0.5 ml per minute. The column is washed to baseline A_{280} with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching A_{280} baseline again, the column is developed with a 0 to 500 mM imidazole gradient in the secondary wash buffer. One ml fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni^{2+}-NTA-conjugated to alkaline phosphatase (Qiagen). Fractions containing the eluted His_{10}-tagged PRO are pooled and dialyzed against loading buffer.

Alternatively, purification of the IgG tagged (or Fc tagged) PRO can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

Following PCR amplification, the respective coding sequences are subcloned into a baculovirus expression vector (pb.PH.IgG for IgG fusions and pb.PH.His.c for poly-His tagged proteins), and the vector and Baculogold® baculovirus DNA (Pharmingen) are co-transfected into 105 *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711), using Lipofectin (Gibco BRL). pb.PH.IgG and pb.PH.His are modifications of the commercially available baculovirus expression vector pVL1393 (Pharmingen), with modified polylinker regions to include the His or Fc tag sequences. The cells are grown in Hink's TNM-FH medium supplemented with 10% FBS (Hyclone). Cells are

incubated for 5 days at 28°C. The supernatant is harvested and subsequently used for the first viral amplification by infecting Sf9 cells in Hink's TNM-FH medium supplemented with 10% FBS at an approximate multiplicity of infection (MOI) of 10. Cells are incubated for 3 days at 28°C. The supernatant is harvested and the expression of the constructs in the baculovirus expression vector is determined by batch binding of 1 ml of supernatant to 25 ml of Ni^{2+}-NTA beads (QIAGEN) for histidine tagged proteins or Protein-A Sepharose CL-4B beads (Pharmacia) for IgG tagged proteins followed by SDS-PAGE analysis comparing to a known concentration of protein standard by Coomassie blue staining.

The first viral amplification supernatant is used to infect a spinner culture (500 ml) of Sf9 cells grown in ESF-921 medium (Expression Systems LLC) at an approximate MOI of 0.1. Cells are incubated for 3 days at 28°C. The supernatant is harvested and filtered. Batch binding and SDS-PAGE analysis is repeated, as necessary, until expression of the spinner culture is confirmed.

The conditioned medium from the transfected cells (0.5 to 3 L) is harvested by centrifugation to remove the cells and filtered through 0.22 micron filters. For the poly-His tagged constructs, the protein construct is purified using a Ni^{2+}-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni^{2+}-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc containing) constructs of proteins are purified from the conditioned media as follows. The conditioned media is pumped onto a 5 ml Protein A column (Pharmacia) which has been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 ml of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity of the proteins is verified by SDS polyacrylamide gel (PEG) electrophoresis and N-terminal amino acid sequencing by Edman degradation.

Alternatively, a modified baculovirus procedure may be used incorporating high-5 cells. In this procedure, the DNA encoding the desired sequence is amplified with suitable systems, such as Pfu (Stratagene), or fused upstream (5'-of) of an epitope tag contained with a baculovirus expression vector. Such epitope tags include poly-His tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pIE1-1 (Novagen). The pIE1-1 and pIE1-2 vectors are designed for constitutive expression of recombinant proteins from the baculovirus ie1 promoter in stably-transformed insect cells (1). The plasmids differ only in the orientation of the multiple cloning sites and contain all promoter sequences known to be important for ie1-mediated gene expression in uninfected insect cells as well as the hr5 enhancer element. pIE1-1 and pIE1-2 include the translation initiation site and can be used to produce fusion proteins. Briefly, the desired sequence or the desired portion of the sequence (such as the sequence encoding the

extracellular domain of a transmembrane protein) is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector. For example, derivatives of pIE1-1 can include the Fc region of human IgG (pb.PH.IgG) or an 8 histidine (pb.PH.His) tag downstream (3'-of) the desired sequence. Preferably, the vector construct is sequenced for confirmation.

High-5 cells are grown to a confluency of 50% under the conditions of, 27°C, no CO_2, NO pen/strep. For each 150 mm plate, 30 μg of pIE based vector containing the sequence is mixed with 1 ml Ex-Cell medium (Media: Ex-Cell 401 + 1/100 L-Glu JRH Biosciences #14401-78P (note: this media is light sensitive)), and in a separate tube, 100 μl of CellFectin (CellFECTIN (GibcoBRL #10362-010) (vortexed to mix)) is mixed with 1 ml of Ex-Cell medium. The two solutions are combined and allowed to incubate at room temperature for 15 minutes. 8 ml of Ex-Cell media is added to the 2 ml of DNA/CellFECTIN mix and this is layered on high-5 cells that have been washed once with Ex-Cell media. The plate is then incubated in darkness for 1 hour at room temperature. The DNA/CellFECTIN mix is then aspirated, and the cells are washed once with Ex-Cell to remove excess CellFECTIN, 30 ml of fresh Ex-Cell media is added and the cells are incubated for 3 days at 28°C. The supernatant is harvested and the expression of the sequence in the baculovirus expression vector is determined by batch binding of 1 ml of supernatent to 25 ml of Ni^{2+}-NTA beads (QIAGEN) for histidine tagged proteins or Protein-A Sepharose CL-4B beads (Pharmacia) for IgG tagged proteins followed by SDS-PAGE analysis comparing to a known concentration of protein standard by Coomassie blue staining.

The conditioned media from the transfected cells (0.5 to 3 L) is harvested by centrifugation to remove the cells and filtered through 0.22 micron filters. For the poly-His tagged constructs, the protein comprising the sequence is purified using a Ni^{2+}-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni^{2+}-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 48°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is then subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

Immunoadhesin (Fc containing) constructs of proteins are purified from the conditioned media as follows. The conditioned media is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 ml of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity of the sequence is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation and other analytical procedures as desired or necessary.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

6.11. EXAMPLE 11: Preparation of Antibodies that Bind PRO

This example illustrates preparation of monoclonal antibodies which can specifically bind the PRO polypeptide or an epitope on the PRO polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, *supra*. Immunogens that may be employed include purified PRO, fusion proteins containing PRO, and cells expressing recombinant PRO on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

Mice, such as Balb/c, are immunized with the PRO immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice by retro-orbital bleeding for testing in ELISA assays to detect anti-PRO antibodies.

After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of PRO. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against PRO. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against PRO is within the skill in the art.

The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-PRO monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

6.12. EXAMPLE 12: Purification of PRO Polypeptides Using Specific Antibodies

Native or recombinant PRO polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-PRO polypeptide, mature PRO polypeptide, or pre-PRO polypeptide is purified by immunoaffinity chromatography using antibodies specific for the PRO polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-PRO polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise,

monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of PRO polypeptide by preparing a fraction from cells containing PRO polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble PRO polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble PRO polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PRO polypeptide (*e.g.*, high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/PRO polypeptide binding (*e.g.*, a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and PRO polypeptide is collected.

6.13. EXAMPLE 13: Drug Screening

This invention is particularly useful for screening compounds by using PRO polypeptides or binding fragment thereof in any of a variety of drug screening techniques. The PRO polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the PRO polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between PRO polypeptide or a fragment and the agent being tested. Alternatively, one can examine the diminution in complex formation between the PRO polypeptide and its target cell or target receptors caused by the agent being tested.

Thus, the present invention provides methods of screening for drugs or any other agents which can affect a PRO polypeptide-associated disease or disorder. These methods comprise contacting such an agent with an PRO polypeptide or fragment thereof and assaying (I) for the presence of a complex between the agent and the PRO polypeptide or fragment, or (ii) for the presence of a complex between the PRO polypeptide or fragment and the cell, by methods well known in the art. In such competitive binding assays, the PRO polypeptide or fragment is typically labeled. After suitable incubation, free PRO polypeptide or fragment is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular agent to bind to PRO polypeptide or to interfere with the PRO polypeptide/cell complex.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to a polypeptide and is described in detail in WO 84/03564, published on September 13, 1984. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such

as plastic pins or some other surface. As applied to a PRO polypeptide, the peptide test compounds are reacted with PRO polypeptide and washed. Bound PRO polypeptide is detected by methods well known in the art. Purified PRO polypeptide can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding PRO polypeptide specifically compete with a test compound for binding to PRO polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PRO polypeptide.

6.14. EXAMPLE 14: Rational Drug Design

The goal of rational drug design is to produce structural analogs of biologically active polypeptide of interest (*i.e.*, a PRO polypeptide) or of small molecules with which they interact, *e.g.*, agonists, antagonists, or inhibitors. Any of these examples can be used to fashion drugs which are more active or stable forms of the PRO polypeptide or which enhance or interfere with the function of the PRO polypeptide *in vivo* (*c.f.*, Hodgson, Bio/Technology, 9: 19-21 (1991)).

In one approach, the three-dimensional structure of the PRO polypeptide, or of an PRO polypeptide-inhibitor complex, is determined by x-ray crystallography, by computer modeling or, most typically, by a combination of the two approaches. Both the shape and charges of the PRO polypeptide must be ascertained to elucidate the structure and to determine active site(s) of the molecule. Less often, useful information regarding the structure of the PRO polypeptide may be gained by modeling based on the structure of homologous proteins. In both cases, relevant structural information is used to design analogous PRO polypeptide-like molecules or to identify efficient inhibitors. Useful examples of rational drug design may include molecules which have improved activity or stability as shown by Braxton and Wells, Biochemistry, 31:7796-7801 (1992) or which act as inhibitors, agonists, or antagonists of native peptides as shown by Athauda *et al.*, J. Biochem., 113:742-746 (1993).

It is also possible to isolate a target-specific antibody, selected by functional assay, as described above, and then to solve its crystal structure. This approach, in principle, yields a pharmacore upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced peptides. The isolated peptides would then act as the pharmacore.

By virtue of the present invention, sufficient amounts of the PRO polypeptide may be made available to perform such analytical studies as X-ray crystallography. In addition, knowledge of the PRO polypeptide amino acid sequence provided herein will provide guidance to those employing computer modeling techniques in place of or in addition to x-ray crystallography.

6.15. EXAMPLE 15: Stimulation of Endothelial Cell Proliferation (Assay 8)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to stimulate adrenal cortical capillary endothelial cell (ACE) growth. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of conditions or disorders where angiogenesis would be beneficial including, for example, wound healing, and the like (as would agonists of these PRO polypeptides). Antagonists of the PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of cancerous tumors.

Bovine adrenal cortical capillary endothelial (ACE) cells (from primary culture, maximum of 12-14 passages) were plated in 96-well plates at 500 cells/well per 100 microliter. Assay media included low glucose DMEM, 10% calf serum, 2 mM glutamine, and 1X penicillin/streptomycin/fungizone. Control wells included the following: (1) no ACE cells added; (2) ACE cells alone; (3) ACE cells plus VEGF (5 ng/ml); and (4) ACE cells plus FGF (5ng/ml). The control or test sample, (in 100 microliter volumes), was then added to the wells (at dilutions of 1%, 0.1% and 0.01%, respectively). The cell cultures were incubated for 6-7 days at 37°C/5% CO_2. After the incubation, the media in the wells was aspirated, and the cells were washed 1X with PBS. An acid phosphatase reaction mixture (100 microliter; 0.1M sodium acetate, pH 5.5, 0.1% Triton X-100, 10 mM p-nitrophenyl phosphate) was then added to each well. After a 2 hour incubation at 37°C, the reaction was stopped by addition of 10 microliters 1N NaOH. Optical density (OD) was measured on a microplate reader at 405 nm.

The activity of a PRO polypeptide was calculated as the fold increase in proliferation (as determined by the acid phosphatase activity, OD 405 nm) relative to (1) cell only background, and (2) relative to maximum stimulation by VEGF. VEGF (at 3-10 ng/ml) and FGF (at 1-5 ng/ml) were employed as an activity reference for maximum stimulation. Results of the assay were considered "positive" if the observed stimulation was ≥ 50% increase over background. VEGF (5 ng/ml) control at 1% dilution gave 1.24 fold stimulation; FGF (5 ng/ml) control at 1% dilution gave 1.46 fold stimulation.

PRO21 tested positive in this assay.

6.16. EXAMPLE 16: Inhibition of Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth (Assay 9)

The ability of various PRO polypeptides to inhibit VEGF stimulated proliferation of endothelial cells was tested. Polypeptides testing positive in this assay are useful for inhibiting endothelial cell growth in mammals where such an effect would be beneficial, e.g., for inhibiting tumor growth.

Specifically, bovine adrenal cortical capillary endothelial cells (ACE) (from primary culture, maximum of 12-14 passages) were plated in 96-well plates at 500 cells/well per 100 microliter. Assay media included low glucose DMEM, 10% calf serum, 2 mM glutamine, and 1X penicillin/streptomycin/fungizone. Control wells included the following: (1) no ACE cells added; (2) ACE cells alone; (3) ACE cells plus 5 ng/ml FGF; (4) ACE cells plus 3 ng/ml VEGF; (5) ACE cells plus 3 ng/ml VEGF plus 1 ng/ml TGF-beta; and (6) ACE cells plus 3 ng/ml VEGF plus 5 ng/ml LIF. The test samples, poly-his tagged PRO polypeptides (in 100 microliter volumes), were then added to the wells (at dilutions of 1%, 0.1% and 0.01%, respectively). The cell cultures were

incubated for 6-7 days at 37°C/5% CO_2. After the incubation, the media in the wells was aspirated, and the cells were washed 1X with PBS. An acid phosphatase reaction mixture (100 microliter; 0.1M sodium acetate, pH 5.5, 0.1% Triton X-100, 10 mM p-nitrophenyl phosphate) was then added to each well. After a 2 hour incubation at 37°C, the reaction was stopped by addition of 10 microliters 1N NaOH. Optical density (OD) was measured on a microplate reader at 405 nm.

The activity of PRO polypeptides was calculated as the percent inhibition of VEGF (3 ng/ml) stimulated proliferation (as determined by measuring acid phosphatase activity at OD 405 nm) relative to the cells without stimulation. TGF-beta was employed as an activity reference at 1 ng/ml, since TGF-beta blocks 70-90% of VEGF-stimulated ACE cell proliferation. The results are indicative of the utility of the PRO polypeptides in cancer therapy and specifically in inhibiting tumor angiogenesis. Numerical values (relative inhibition) are determined by calculating the percent inhibition of VEGF stimulated proliferation by the PRO polypeptides relative to cells without stimulation and then dividing that percentage into the percent inhibition obtained by TGF-β at 1 ng/ml which is known to block 70-90% of VEGF stimulated cell proliferation. The results are considered positive if the PRO polypeptide exhibits 30% or greater inhibition of VEGF stimulation of endothelial cell growth (relative inhibition 30% or greater).

PRO247, PRO720 and PRO4302 tested positive in this assay.

6.17. EXAMPLE 17: Enhancement of Heart Neonatal Hypertrophy Induced by LIF+ET-1 (Assay 75)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to enhance neonatal heart hypertrophy induced by LIF and endothelin-1 (ET-1). A test compound that provides a positive response in the present assay would be useful for the therapeutic treatment of cardiac insufficiency diseases or disorders characterized or associated with an undesired level of hypertrophy of the cardiac muscle.

Cardiac myocytes from 1-day old Harlan Sprague Dawley rats (180 μl at 7.5 x 10^4/ml, serum <0.1, freshly isolated) are introduced on day 1 to 96-well plates previously coated with DMEM/F12 + 4%FCS. Test PRO polypeptide samples or growth medium alone (negative control) are then added directly to the wells on day 2 in 20 μl volume. LIF + ET-1 are then added to the wells on day 3. The cells are stained after an additional 2 days in culture and are then scored visually the next day. A positive in the assay occurs when the PRO polypeptide treated myocytes obtain a score greater than zero. A score of zero represents non-responsive cells whereas scores of 1 or 2 represent enhancement (*i.e.* they are visually larger on the average or more numerous than the untreated myocytes).

PRO21 polypeptides tested positive in this assay.

6.18. EXAMPLE 18: Detection of Endothelial Cell Apoptosis (FACS) (Assay 96)

The ability of PRO polypeptides of the present invention to induce apoptosis in endothelial cells was tested in human venous umbilical vein endothelial cells (HUVEC, Cell Systems) in gelatinized T175 flasks using HUVEC cells below passage 10. PRO polypeptides testing positive in this assay are expected to be useful for

therapeutically treating conditions where apoptosis of endothelial cells would be beneficial including, for example, the therapeutic treatment of tumors.

On day one, the cells were split [420,000 cells per gelatinized 6 cm dishes - (11 x 10^3 cells/cm^2 Falcon, Primaria)] and grown in media containing serum (CS-C, Cell System) overnight or for 16 hours to 24 hours.

On day 2, the cells were washed 1x with 5 ml PBS ; 3 ml of 0% serum medium was added with VEGF (100 ng/ml); and 30 μl of the PRO test compound (final dilution 1%) or 0% serum medium (negative control) was added. The mixtures were incubated for 48 hours before harvesting.

The cells were then harvested for FACS analysis. The medium was aspirated and the cells washed once with PBS. 5 ml of 1 x trypsin was added to the cells in a T-175 flask, and the cells were allowed to stand until they were released from the plate (about 5-10 minutes). Trypsinization was stopped by adding 5 ml of growth media. The cells were spun at 1000 rpm for 5 minutes at 4°C. The media was aspirated and the cells were resuspended in 10 ml of 10% serum complemented medium (Cell Systems), 5 μl of Annexin-FITC (BioVison) added and chilled tubes were submitted for FACS. A positive result was determined to be enhanced apoptosis in the PRO polypeptide treated samples as compared to the negative control.

PRO4302 polypeptide tested positive in this assay.

6.19. EXAMPLE 19: Induction of c-fos in HUVEC Cells (Assay 123)

This assay is designed to determine whether PRO polypeptides show the ability to induce c-fos in HUVEC cells. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of conditions or disorders where angiogenesis would be beneficial including, for example, wound healing, and the like (as would agonists of these PRO polypeptides). Antagonists of the PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of cancerous tumors.

Human venous umbilical vein endothelial cells (HUVEC, Cell Systems) in growth media (50% Ham's F12 w/o GHT: low glucose, and 50% DMEM without glycine: with NaHCO3, 1% glutamine, 10 mM HEPES, 10% FBS, 10 ng/ml bFGF) were plated on 96-well microtiter plates at a cell density of 5x10^3 cells/well. The day after plating (day 2), the cells were starved for 24 hours by removing the growth media and replacing with serum free media. On day 3, the cells are treated with 100 μl/well test samples and controls (positive control = growth media; negative control = Protein 32 buffer = 10 mM HEPES, 140 mM NaCl, 4% (w/v) mannitol, pH 6.8). One plate of cells was incubated for 30 minutes at 37°C, in 5% CO_2. Another plate of cells was incubated for 60 minutes at 37°C, in 5% CO_2. The samples were removed, and RNA was harvested using the RNeasy 96 kit (Qiagen). Next, the RNA was assayed for c-fos, egr-1 and GAPDH induction using Taqman.

The measure of activity of the fold increase over the negative control (Protein 32/HEPES buffer described above) value was by obtained by calculating the fold increase of the ratio of c-fos to GAPDH in test samples as compared to the negative control. The results are considered positive if the PRO polypeptide exhibits at least a two-fold value over the negative buffer control.

PRO1376 polypeptide tested positive in this assay.

6.20. EXAMPLE 20: Normal Human Iliac Artery Endothelial Cell Proliferation (Assay 138)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to induce proliferation of human iliac artery endothelial cells in culture and, therefore, function as useful growth factors.

On day 0, human iliac artery endothelial cells (from cell lines, maximum of 12-14 passages) were plated in 96-well plates at 1000 cells/well per 100 microliter and incubated overnight in complete media [epithelial cell growth media (EGM, Clonetics), plus supplements: human epithelial growth factor (hEGF), bovine brain extract (BBE), hydrocortisone, GA-1000, and fetal bovine serum (FBS, Clonetics)]. On day 1, complete media was replaced by basal media [EGM plus 1% FBS] and addition of PRO polypeptides at 1%, 0.1% and 0.01%. On day 7, an assessment of cell proliferation was performed by Alamar Blue assay followed by Crystal Violet. Results are expresses as % of the cell growth observed with control buffer.

The following PRO polypeptides tested positive in this assay: PRO214, PRO238, PRO256, PRO363, PRO365, PRO791, PRO836, PRO1025, PRO1029, PRO1186, PRO1192, PRO1272, PRO1274, PRO1279, PRO1306, PRO1325, PRO1329, PRO1376, PRO1411, PRO1419, PRO1508, PRO1787, PRO1868, PRO1890, PRO4324, PRO4333, PRO4408, PRO4499, PRO5725, PRO6006, PRO9821, PRO9873, PRO10008, PRO10096, PRO19670, PRO20040, PRO20044, PRO21384 and PRO28631.

6.21. EXAMPLE 21: Pooled Human Umbilical Vein Endothelial Cell Proliferation (Assay 139)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to induce proliferation of pooled human umbilical vein endothelial cells in culture and, therefore, function as useful growth factors.

On day 0, pooled human umbilical vein endothelial cells (from cell lines, maximum of 12-14 passages) were plated in 96-well plates at 1000 cells/well per 100 microliter and incubated overnight in complete media [epithelial cell growth media (EGM, Clonetics), plus supplements: human epithelial growth factor (hEGF), bovine brain extract (BBE), hydrocortisone, GA-1000, and fetal bovine serum (FBS, Clonetics)]. On day 1, complete media was replaced by basal media [EGM plus 1% FBS] and addition of PRO polypeptides at 1%, 0.1% and 0.01%. On day 7, an assessment of cell proliferation was performed by Alamar Blue assay followed by Crystal Violet. Results are expresses as % of the cell growth observed with control buffer.

The following PRO polypeptides tested positive in this assay: PRO181, PRO205, PRO221, PRO229, PRO231, PRO238, PRO241, PRO247, PRO256, PRO258, PRO263, PRO265, PRO295, PRO321, PRO322, PRO337, PRO363, PRO444, PRO533, PRO697, PRO725, PRO771, PRO788, PRO819, PRO827, PRO828, PRO846, PRO865, PRO1005, PRO1006, PRO1007, PRO1025, PRO1054, PRO1071, PRO1075, PRO1079, PRO1080, PRO1114, PRO1131, PRO1155, PRO1160, PRO1184, PRO1190, PRO1192, PRO1195, PRO1244, PRO1272, PRO1273, PRO1279, PRO1283, PRO1286, PRO1306, PRO1309, PRO1325, PRO1329, PRO1347, PRO1356, PRO1376, PRO1382, PRO1412, PRO1419, PRO1474, PRO1477, PRO1488, PRO1550, PRO1556, PRO1760, PRO1782, PRO1787, PRO1801, PRO1868, PRO1887, PRO3438, PRO3444, PRO4302, PRO4324, PRO4341, PRO4342, PRO4353, PRO4354, PRO4356, PRO4371, PRO4405, PRO4422, PRO4425, PRO5723,

PRO5725, PRO5737, PRO5776, PRO6029, PRO6071, PRO7436, PRO9771, PRO10008, PRO10096, PRO21055 and PRO21384.

6.22. EXAMPLE 22: Human Coronary Artery Smooth Muscle Cell Proliferation (Assay 140)

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to induce proliferation of human coronary artery smooth muscle cells in culture and, therefore, function as useful growth factors.

On day 0, human coronary artery smooth muscle cells (from cell lines, maximum of 12-14 passages) were plated in 96-well plates at 1000 cells/well per 100 microliter and incubated overnight in complete media [smooth muscle growth media (SmGM, Clonetics), plus supplements: insulin, human epithelial growth factor (hEGF), human fibroblast growth factor (hFGF), GA-1000, and fetal bovine serum (FBS, Clonetics)]. On day 1, complete media was replaced by basal media [SmGM plus 1% FBS] and addition of PRO polypeptides at 1%, 0.1% and 0.01%. On day 7, an assessment of cell proliferation was performed by Alamar Blue assay followed by Crystal Violet. Results are expresses as % of the cell growth observed with control buffer.

The following PRO polypeptides tested positive in this assay: PRO162, PRO181, PRO182, PRO195, PRO204, PRO221, PRO230, PRO256, PRO258, PRO533, PRO697, PRO725, PRO738, PRO826, PRO836, PRO840, PRO846, PRO865, PRO982, PRO1025, PRO1029, PRO1071, PRO1080, PRO1083, PRO1134, PRO1160, PRO1182, PRO1184, PRO1186, PRO1192, PRO1265, PRO1274, PRO1279, PRO1283, PRO1306, PRO1308, PRO1309, PRO1325, PRO1337, PRO1338, PRO1343, PRO1376, PRO1387, PRO1411, PRO1412, PRO1415, PRO1434, PRO1474, PRO1488, PRO1550, PRO1556, PRO1567, PRO1600, PRO1754, PRO1758, PRO1760, PRO1787, PRO1865, PRO1868, PRO1917, PRO1928, PRO3438, PRO3562, PRO4302, PRO4333, PRO4345, PRO4353, PRO4354, PRO4405, PRO4408, PRO4430, PRO4503, PRO5725, PRO6714, PRO9771, PRO9820, PRO9940, PRO10096, PRO21055, PRO21184 and PRO21366.

6.23. EXAMPLE 23: Microarray Analysis to Detect Overexpression of PRO Polypeptides in HUVEC Cells Treated with Growth Factors

This assay is designed to determine whether PRO polypeptides of the present invention show the ability to induce angiogenesis by stimulating endothelial cell tube formation in HUVEC cells.

Nucleic acid microarrays, often containing thousands of gene sequences, are useful for identifying differentially expressed genes in tissues exposed to various stimuli (*e.g.*, growth factors) as compared to their normal, unexposed counterparts. Using nucleic acid microarrays, test and control mRNA samples from test and control tissue samples are reverse transcribed and labeled to generate cDNA probes. The cDNA probes are then hybridized to an array of nucleic acids immobilized on a solid support. The array is configured such that the sequence and position of each member of the array is known. Hybridization of a labeled probe with a particular array member indicates that the sample from which the probe was derived expresses that gene. If the hybridization signal of a probe from a test (exposed tissue) sample is greater than hybridization signal of a probe from a control (normal, unexposed tissue) sample, the gene or genes overexpressed in the exposed tissue are identified. The

implication of this result is that an overexpressed protein in an exposed tissue may be involved in the functional changes within the tissue following exposure to the stimuli (*e.g.*, tube formation).

The methodology of hybridization of nucleic acids and microarray technology is well known in the art. In the present example, the specific preparation of nucleic acids for hybridization and probes, slides, and hybridization conditions are all detailed in U.S. Provisional Patent Application Serial No. 60/193,767, filed on March 31, 2000 and which is herein incorporated by reference.

In the present example, HUVEC cells grown in either collagen gels or fibrin gels were induced to form tubes by the addition of various growth factors. Specifically, collagen gels were prepared as described previously in Yang *et al.*, *American J. Pathology*, 1999, 155(3):887-895 and Xin *et al.*,*American J. Pathology*, 2001, 158(3):1111-1120. Following gelation of the HUVEC cells, 1X basal medium containing M199 supplemented with 1%FBS, 1X ITS, 2 mM L-glutamine, 50 μg/ml ascorbic acid, 26.5 mM $NaHCO_3$, 100U/ml penicillin and 100 U/ml streptomycin was added. Tube formation was elicited by the inclusion in the culture media of either a mixture of phorbol myrsitate acetate (50 nM), vascular endothelial cell growth factor (40 ng/ml) and basic fibroblast growth factor (40 ng/ml) ("PMA growth factor mix") or hepatocyte growth factor (40 ng/ml) and vascular endothelial cell growth factor (40 ng/ml) (HGF/VEGF mix) for the indicated period of time. Fibrin Gels were prepared by suspending Huvec (4 x 10^5 cells/ml) in M199 containing 1% fetal bovine serum (Hyclone) and human fibrinogen (2.5mg/ml). Thrombin (50U/ml) was then added to the fibrinogen suspension at a ratio of 1 part thrombin solution:30 parts fibrinogen suspension. The solution was then layered onto 10 cm tissue culture plates (total volume: 15 ml/plate) and allowed to solidify at 37°C for 20 min. Tissue culture media (10 ml of BM containing PMA (50 nM), bFGF (40ng/ml) and VEGF (40 ng/ml)) was then added and the cells incubated at 37°C in 5%CO_2 in air for the indicated period of time.

Total RNA was extracted from the HUVEC cells incubated for 0, 4, 8, 24, 40 and 50 hours in the different matrix and media combinations using a TRIzol extraction followed by a second purification using RNAeasy Mini Kit (Qiagen). The total RNA was used to prepare cRNA which was then hybridized to the microarrays.

In the present experiments, nucleic acid probes derived from the herein described PRO polypeptide-encoding nucleic acid sequences were used in the creation of the microarray and RNA from the HUVEC cells described above were used for the hybridization thereto. Pairwise comparisons were made using time 0 chips as a baseline. Three replicate samples were analyzed for each experimental condition and time. Hence there were 3 time 0 samples for each treatment and 3 replicates of each successive time point. Therefore, a 3 by 3 comparison was performed for each time point compared against each time 0 point. This resulted in 9 comparisons per time point. Only those genes that had increased expression in all three non-time-0 replicates in each of the different matrix and media combinations as compared to any of the three time zero replicates were considered positive. Although this stringent method of data analysis does allow for false negatives, it minimizes false positives.

PRO178, PRO195, PRO228, PRO301, PRO302, PRO532, PRO724, PRO730, PRO734, PRO793, PRO871, PRO938, PRO1012, PRO1120, PRO1139, PRO1198, PRO1287, PRO1361, PRO1864, PRO1873,

PRO2010, PRO3579, PRO4313, PRO4527, PRO4538, PRO4553, PRO4995, PRO5730, PRO6008, PRO7223, PRO7248 and PRO7261 tested positive in this assay.

6.24. EXAMPLE 24: *In situ* Hybridization

In situ hybridization is a powerful and versatile technique for the detection and localization of nucleic acid sequences within cell or tissue preparations. It may be useful, for example, to identify sites of gene expression, analyze the tissue distribution of transcription, identify and localize viral infection, follow changes in specific mRNA synthesis, and aid in chromosome mapping.

In situ hybridization was performed following an optimized version of the protocol by Lu and Gillett, Cell Vision, 1: 169-176 (1994), using PCR-generated ^{33}P-labeled riboprobes. Briefly, formalin-fixed, paraffin-embedded human tissues were sectioned, deparaffinized, deproteinated in proteinase K (20 g/ml) for 15 minutes at 37°C, and further processed for *in situ* hybridization as described by Lu and Gillett, *supra*. A (^{33}-P)UTP-labeled antisense riboprobe was generated from a PCR product and hybridized at 55°C overnight. The slides were dipped in Kodak NTB2™ nuclear track emulsion and exposed for 4 weeks.

6.24.1. ^{33}P-Riboprobe synthesis

6.0 μl (125 mCi) of ^{33}P-UTP (Amersham BF 1002, SA<2000 Ci/mmol) were speed-vacuum dried. To each tube containing dried ^{33}P-UTP, the following ingredients were added:

2.0 μl 5x transcription buffer
1.0 μl DTT (100 mM)
2.0 μl NTP mix (2.5 mM: 10 μl each of 10 mM GTP, CTP & ATP + 10 μl H_2O)
1.0 μl UTP (50 μM)
1.0 μl RNAsin
1.0 μl DNA template (1 μg)
1.0 μl H_2O
1.0 μl RNA polymerase (for PCR products T3 = AS, T7 = S, usually)

The tubes were incubated at 37°C for one hour. A total of 1.0 μl RQ1 DNase was added, followed by incubation at 37°C for 15 minutes. A total of 90 μl TE (10 mM Tris pH 7.6/1 mM EDTA pH 8.0) was added, and the mixture was pipetted onto DE81 paper. The remaining solution was loaded in a MICROCON-50™ ultrafiltration unit, and spun using program 10 (6 minutes). The filtration unit was inverted over a second tube and spun using program 2 (3 minutes). After the final recovery spin, a total of 100 μl TE was added, then 1 μl of the final product was pipetted on DE81 paper and counted in 6 ml of BIOFLUOR II™.

The probe was run on a TBE/urea gel. A total of 1-3 μl of the probe or 5 μl of RNA Mrk III was added to 3 μl of loading buffer. After heating on a 95°C heat block for three minutes, the gel was immediately placed on ice. The wells of gel were flushed, and the sample was loaded and run at 180-250 volts for 45 minutes. The gel was wrapped in plastic wrap (SARAN™ brand) and exposed to XAR film with an intensifying screen in a -70°C freezer one hour to overnight.

6.24.2. ^{33}P-Hybridization

6.24.2.1. *Pretreatment of frozen sections*

The slides were removed from the freezer, placed on aluminum trays, and thawed at room temperature for 5 minutes. The trays were placed in a 55°C incubator for five minutes to reduce condensation. The slides were fixed for 10 minutes in 4% paraformaldehyde on ice in the fume hood, and washed in 0.5 x SSC for 5 minutes, at room temperature (25 ml 20 x SSC + 975 ml SQ H_2O). After deproteination in 0.5 μg/ml proteinase K for 10 minutes at 37°C (12.5 μl of 10 mg/ml stock in 250 ml prewarmed RNAse-free RNAse buffer), the sections were washed in 0.5 x SSC for 10 minutes at room temperature. The sections were dehydrated in 70%, 95%, and 100% ethanol, 2 minutes each.

6.24.2.2. *Pretreatment of paraffin-embedded sections*

The slides were deparaffinized, placed in SQ H_2O, and rinsed twice in 2 x SSC at room temperature, for 5 minutes each time. The sections were deproteinated in 20 μg/ml proteinase K (500 μl of 10 mg/ml in 250 ml RNase-free RNase buffer; 37°C, 15 minutes) for human embryo tissue, or 8 x proteinase K (100 μl in 250 ml Rnase buffer, 37°C, 30 minutes) for formalin tissues. Subsequent rinsing in 0.5 x SSC and dehydration were performed as described above.

6.24.2.3. *Prehybridization*

The slides were laid out in a plastic box lined with Box buffer (4 x SSC, 50% formamide) - saturated filter paper. The tissue was covered with 50 μl of hybridization buffer (3.75 g dextran sulfate + 6 ml SQ H_2O), vortexed, and heated in the microwave for 2 minutes with the cap loosened. After cooling on ice, 18.75 ml formamide, 3.75 ml 20 x SSC, and 9 ml SQ H_2O were added, and the tissue was vortexed well and incubated at 42°C for 1-4 hours.

6.24.2.4. *Hybridization*

1.0 x 10^6 cpm probe and 1.0 μl tRNA (50 mg/ml stock) per slide were heated at 95°C for 3 minutes. The slides were cooled on ice, and 48 μl hybridization buffer was added per slide. After vortexing, 50 μl ^{33}P mix was added to 50 μl prehybridization on the slide. The slides were incubated overnight at 55°C.

6.24.2.5. *Washes*

Washing was done for 2x10 minutes with 2xSSC, EDTA at room temperature (400 ml 20 x SSC + 16 ml 0.25 M EDTA, V_f=4L), followed by RNAseA treatment at 37°C for 30 minutes (500 μl of 10 mg/ml in 250 ml Rnase buffer = 20 μg/ml), The slides were washed 2 x10 minutes with 2 x SSC, EDTA at room temperature. The stringency wash conditions were as follows: 2 hours at 55°C, 0.1 x SSC, EDTA (20 ml 20 x SSC + 16 ml EDTA, V_f=4L).

6.24.2.6. *Oligonucleotides*

In situ analysis was performed on three of the DNA sequences disclosed herein. The primers used to generate the probes and/or the probes employed for these analyses are as follows:

DNA33100-p1: 5'GGA TTC TAA TAC GAC TCA CTA TAG GGC CGG GTG GAG GTG GAA CAG AAA 3' (SEQ ID NO:375)

DNA33100-p2: 5' CTA TGA AAT TAA CCC TCA CTA AAG GGA CAC AGA CAG AGC CCC ATA CGC 3' (SEQ ID NO:376)

DNA34431-p1: 5'GGA TTC TAA TAC GAC TCA CTA TAG GGC CAG GGA AAT CCG GAT GTC TC 3' (SEQ ID NO:377)

DNA34431-p2: 5' CTA TGA AAT TAA CCC TCA CTA AAG GGA GTA AGG GGA TGC CAC CGA GTA 3' (SEQ ID NO:378)

DNA38268-p1: 5'GGA TTC TAA TAC GAC TCA CTA TAG GGC CAG CTA CCC GCA GGA GGA GG 3' (SEQ ID NO:379)

DNA38268-p2: 5'CTA TGA AAT TAA CCC TCA CTA AAG GGA TCC CAG GTG ATG AGG TCC AGA 3' (SEQ ID NO:380)

DNA64908 probe: 5'CCATCTCGGAGACCTTTGTGCAGCGTGTATACCAGCCTTACCTCACCA CTTGCGACGGACACAGAGCCTGCAGCACCTACCGAACCATCTACCGGAC TGCCTATCGCCGTAGCCCTGGGGTGACTCCCGCAAGCCTCGCTATGCTTG CTGCCCTGGTTGGAAGAGGACCAGTGGGCTCCCTGGGGCTTGTGGAGCA GCAATATGCCAGCCTCCATGTGGGAATGGAGGGAGTTGCATCCGCCCAG GACACTGCCGCTGCCCTGTGGGATGGCAGGGAGATACTTGCCAGACAGA TGTTGATGAATGCAGTACAGGAGAGGCCAGTTGTCCCCAGCGCTGTGTC AATACTGTGGGAAGTTACTGGTGCCAGGGATGGGAGGGACAAAGCCCAT CTGCAGATGGGACGCGCTGCCTGTCTAAGGAGGGGCCCTCCCGGTGGCC CCAACCCCACAGCAGGAGTGGACAGCA3' (SEQ ID NO:381)

6.24.2.7. *Results*

In situ analysis was performed and the results from these analyses are as follows:

6.24.2.7.1. DNA33100-1159 (PRO229) (Scavenger-R/CD6 homologTNF motif)

A specific positive signal was observed in mononuclear phagocytes (macrophages) of fetal and adult spleen, liver, lymph node and thymus. All other tissues were negative.

6.24.2.7.2. DNA34431-1177 (PRO263) (CD44)

A specific positive signal was observed in human fetal tissues and placenta over mononuclear cells, with strong expression in epithelial cells of the adrenal cortex. All adult tissues were negative.

6.24.2.7.3. DNA38268-1188 (PRO295) (Integrin)

A specific positive signal was observed in human fetal ganglion cells, fetal neurons, adult adrenal medulla and adult neurons. All other tissues were negative.

6.24.2.7.4. DNA64908-1163-1 (PRO1449)

A specific positive signal was observed in the developing vasculature (from E7-E11), in endothelial cells and in progenitors of endothelial cells in wholemount in situ hybridizations of mouse embryos (Figure 375). Specific expression was also observed in a subset of blood vessels and epidermis from E12 onward. A mouse orthologue of PRO1449 which has about 78% amino acid identity with PRO1449 was used as the probe.

In normal adult tissues, expression was low to absent. When present, expression was confined to the vasculature (Figure 376). Figure 376 further shows that highest expression in adult tissues was observed regionally in vessels running within the white matter of the brain. Elevated expression was also observed in vasculature of many inflamed and diseased tissues, including, but not limited to, tumor vasculature.

Following electroporation of the mouse orthologue of PRO1449 into the choroid layer in the eyes of chicken embryos, new vessel formation was observed in the electroporated eye (top right), but not in the control side from the same embryo (top left), or an embryo that was electroporated with a control cDNA (bottom right) (Figure 377).

The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The present invention is not to be limited in scope by the construct(s) deposited, since the deposited embodiment(s) is/are intended as single illustration(s) of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material(s) herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. An isolated nucleic acid molecule having at least 80% nucleic acid sequence identity to a nucleotide sequence that encodes an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure

248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) and Figure 374 (SEQ ID NO:374).

2. An isolated nucleic acid molecule having at least 80% nucleic acid sequence identity to a nucleotide sequence selected from the group consisting of the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), Figure 105 (SEQ ID NO:105), Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ

ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161), Figure 163 (SEQ ID NO:163), Figure 165 (SEQ ID NO:165), Figure 167 (SEQ ID NO:167), Figure 169 (SEQ ID NO:169), Figure 171 (SEQ ID NO:171), Figure 173 (SEQ ID NO:173), Figure 175 (SEQ ID NO:175), Figure 177 (SEQ ID NO:177), Figure 179 (SEQ ID NO:179), Figure 181 (SEQ ID NO:181), Figure 183 (SEQ ID NO:183), Figure 185 (SEQ ID NO:185), Figure 187 (SEQ ID NO:187), Figure 189 (SEQ ID NO:189), Figure 191 (SEQ ID NO:191), Figure 193 (SEQ ID NO:193), Figure 195 (SEQ ID NO:195), Figure 197 (SEQ ID NO:197), Figure 199 (SEQ ID NO:199), Figure 201 (SEQ ID NO:201), Figure 203 (SEQ ID NO:203), Figure 205 (SEQ ID NO:205), Figure 207 (SEQ ID NO:207), Figure 209 (SEQ ID NO:209), Figure 211 (SEQ ID NO:211), Figure 213 (SEQ ID NO:213), Figure 215 (SEQ ID NO:215), Figure 217 (SEQ ID NO:217), Figure 219 (SEQ ID NO:219), Figure 221 (SEQ ID NO:221), Figure 223 (SEQ ID NO:223), Figure 225 (SEQ ID NO:225), Figure 227 (SEQ ID NO:227), Figure 229 (SEQ ID NO:229), Figure 231 (SEQ ID NO:231), Figure 233 (SEQ ID NO:233), Figure 235 (SEQ ID NO:235), Figure 237 (SEQ ID NO:237), Figure 239 (SEQ ID NO:239), Figure 241 (SEQ ID NO:241), Figure 243 (SEQ ID NO:243), Figure 245 (SEQ ID NO:245), Figure 247 (SEQ ID NO:247), Figure 249 (SEQ ID NO:249), Figure 251 (SEQ ID NO:251), Figure 253 (SEQ ID NO:253), Figure 255 (SEQ ID NO:255), Figure 257 (SEQ ID NO:257), Figure 259 (SEQ ID NO:259), Figure 261 (SEQ ID NO:261), Figure 263 (SEQ ID NO:263), Figure 265 (SEQ ID NO:265), Figure 267 (SEQ ID NO:267), Figure 269 (SEQ ID NO:269), Figure 271 (SEQ ID NO:271), Figure 273 (SEQ ID NO:273), Figure 275 (SEQ ID NO:275), Figure 277 (SEQ ID NO:277), Figure 279 (SEQ ID NO:279), Figure 281 (SEQ ID NO:281), Figure 283 (SEQ ID NO:283), Figure 285 (SEQ ID NO:285), Figure 287 (SEQ ID NO:287), Figures 289A-289B (SEQ ID NO:289), Figure 291 (SEQ ID NO:291), Figure 293 (SEQ ID NO:293), Figure 295 (SEQ ID NO:295), Figure 297 (SEQ ID NO:297), Figure 299 (SEQ ID NO:299), Figure 301 (SEQ ID NO:301), Figure 303 (SEQ ID NO:303), Figure 305 (SEQ ID NO:305), Figure 307 (SEQ ID NO:307), Figure 309 (SEQ ID NO:309), Figures 311A-311B (SEQ ID NO:311), Figure 313 (SEQ ID NO:313), Figure 315 (SEQ ID NO:315), Figure 317 (SEQ ID NO:317), Figure 319 (SEQ ID NO:319), Figure 321 (SEQ ID NO:321), Figure 323 (SEQ ID NO:323), Figure 325 (SEQ ID NO:325), Figure 327 (SEQ ID NO:327), Figure 329 (SEQ ID NO:329), Figure 331 (SEQ ID NO:331), Figure 333 (SEQ ID NO:333), Figure 335 (SEQ ID NO:335), Figure 337 (SEQ ID NO:337), Figure 339 (SEQ ID NO:339), Figure 341 (SEQ ID NO:341), Figure 343 (SEQ ID NO:343), Figure 345 (SEQ ID NO:345), Figure 347 (SEQ ID NO:347), Figure 349 (SEQ ID NO:349), Figures 351A-351B (SEQ ID NO:351), Figure 353 (SEQ ID NO:353), Figure 355 (SEQ ID NO:355), Figure 357 (SEQ ID NO:357), Figure 359 (SEQ ID NO:359), Figure 361 (SEQ ID NO:361), Figure 363 (SEQ ID NO:363), Figure 365 (SEQ ID NO:365), Figure 367 (SEQ ID NO:367), Figure 369 (SEQ ID NO:369), Figure 371 (SEQ ID NO:371) and Figure 373 (SEQ ID NO:373).

3. An isolated nucleic acid molecule having at least 80% nucleic acid sequence identity to a nucleotide sequence selected from the group consisting of the full-length coding sequence of the nucleotide sequence shown in Figure 1 (SEQ ID NO:1), Figure 3 (SEQ ID NO:3), Figure 5 (SEQ ID NO:5), Figure 7 (SEQ ID NO:7), Figure 9 (SEQ ID NO:9), Figure 11 (SEQ ID NO:11), Figure 13 (SEQ ID NO:13), Figure 15 (SEQ ID NO:15), Figure 17 (SEQ ID NO:17), Figure 19 (SEQ ID NO:19), Figure 21 (SEQ ID NO:21), Figure 23 (SEQ ID NO:23), Figure 25 (SEQ ID NO:25), Figure 27 (SEQ ID NO:27), Figure 29 (SEQ ID NO:29), Figure 31 (SEQ ID NO:31), Figure 33 (SEQ ID NO:33), Figure 35 (SEQ ID NO:35), Figure 37 (SEQ ID NO:37), Figure 39 (SEQ ID NO:39), Figure 41 (SEQ ID NO:41), Figure 43 (SEQ ID NO:43), Figure 45 (SEQ ID NO:45), Figure 47 (SEQ ID NO:47), Figure 49 (SEQ ID NO:49), Figure 51 (SEQ ID NO:51), Figure 53 (SEQ ID NO:53), Figure 55 (SEQ ID NO:55), Figure 57 (SEQ ID NO:57), Figure 59 (SEQ ID NO:59), Figure 61 (SEQ ID NO:61), Figure 63 (SEQ ID NO:63), Figure 65 (SEQ ID NO:65), Figure 67 (SEQ ID NO:67), Figure 69 (SEQ ID NO:69), Figure 71 (SEQ ID NO:71), Figure 73 (SEQ ID NO:73), Figures 75A-75B (SEQ ID NO:75), Figure 77 (SEQ ID NO:77), Figure 79 (SEQ ID NO:79), Figure 81 (SEQ ID NO:81), Figure 83 (SEQ ID NO:83), Figure 85 (SEQ ID NO:85), Figure 87 (SEQ ID NO:87), Figure 89 (SEQ ID NO:89), Figure 91 (SEQ ID NO:91), Figure 93 (SEQ ID NO:93), Figure 95 (SEQ ID NO:95), Figure 97 (SEQ ID NO:97), Figure 99 (SEQ ID NO:99), Figure 101 (SEQ ID NO:101), Figure 103 (SEQ ID NO:103), Figure 105 (SEQ ID NO:105), Figure 107 (SEQ ID NO:107), Figure 109 (SEQ ID NO:109), Figure 111 (SEQ ID NO:111), Figure 113 (SEQ ID NO:113), Figure 115 (SEQ ID NO:115), Figure 117 (SEQ ID NO:117), Figure 119 (SEQ ID NO:119), Figure 121 (SEQ ID NO:121), Figure 123 (SEQ ID NO:123), Figure 125 (SEQ ID NO:125), Figure 127 (SEQ ID NO:127), Figure 129 (SEQ ID NO:129), Figure 131 (SEQ ID NO:131), Figure 133 (SEQ ID NO:133), Figure 135 (SEQ ID NO:135), Figure 137 (SEQ ID NO:137), Figure 139 (SEQ ID NO:139), Figure 141 (SEQ ID NO:141), Figure 143 (SEQ ID NO:143), Figure 145 (SEQ ID NO:145), Figure 147 (SEQ ID NO:147), Figure 149 (SEQ ID NO:149), Figure 151 (SEQ ID NO:151), Figure 153 (SEQ ID NO:153), Figure 155 (SEQ ID NO:155), Figure 157 (SEQ ID NO:157), Figure 159 (SEQ ID NO:159), Figure 161 (SEQ ID NO:161), Figure 163 (SEQ ID NO:163), Figure 165 (SEQ ID NO:165), Figure 167 (SEQ ID NO:167), Figure 169 (SEQ ID NO:169), Figure 171 (SEQ ID NO:171), Figure 173 (SEQ ID NO:173), Figure 175 (SEQ ID NO:175), Figure 177 (SEQ ID NO:177), Figure 179 (SEQ ID NO:179), Figure 181 (SEQ ID NO:181), Figure 183 (SEQ ID NO:183), Figure 185 (SEQ ID NO:185), Figure 187 (SEQ ID NO:187), Figure 189 (SEQ ID NO:189), Figure 191 (SEQ ID NO:191), Figure 193 (SEQ ID NO:193), Figure 195 (SEQ ID NO:195), Figure 197 (SEQ ID NO:197), Figure 199 (SEQ ID NO:199), Figure 201 (SEQ ID NO:201), Figure 203 (SEQ ID NO:203), Figure 205 (SEQ ID NO:205), Figure 207 (SEQ ID NO:207), Figure 209 (SEQ ID NO:209), Figure 211 (SEQ ID NO:211), Figure 213 (SEQ ID NO:213), Figure 215 (SEQ ID NO:215), Figure 217 (SEQ ID NO:217), Figure 219 (SEQ ID NO:219), Figure 221 (SEQ ID NO:221), Figure 223 (SEQ ID NO:223), Figure 225 (SEQ ID NO:225), Figure 227 (SEQ ID NO:227), Figure 229 (SEQ ID NO:229), Figure 231 (SEQ ID NO:231), Figure 233 (SEQ ID NO:233), Figure 235 (SEQ ID NO:235), Figure 237 (SEQ ID NO:237), Figure 239 (SEQ ID NO:239), Figure 241 (SEQ ID NO:241), Figure 243 (SEQ ID NO:243), Figure 245 (SEQ ID NO:245), Figure 247 (SEQ ID NO:247), Figure 249 (SEQ ID NO:249), Figure 251 (SEQ ID NO:251), Figure

253 (SEQ ID NO:253), Figure 255 (SEQ ID NO:255), Figure 257 (SEQ ID NO:257), Figure 259 (SEQ ID NO:259), Figure 261 (SEQ ID NO:261), Figure 263 (SEQ ID NO:263), Figure 265 (SEQ ID NO:265), Figure 267 (SEQ ID NO:267), Figure 269 (SEQ ID NO:269), Figure 271 (SEQ ID NO:271), Figure 273 (SEQ ID NO:273), Figure 275 (SEQ ID NO:275), Figure 277 (SEQ ID NO:277), Figure 279 (SEQ ID NO:279), Figure 281 (SEQ ID NO:281), Figure 283 (SEQ ID NO:283), Figure 285 (SEQ ID NO:285), Figure 287 (SEQ ID NO:287), Figures 289A-289B (SEQ ID NO:289), Figure 291 (SEQ ID NO:291), Figure 293 (SEQ ID NO:293), Figure 295 (SEQ ID NO:295), Figure 297 (SEQ ID NO:297), Figure 299 (SEQ ID NO:299), Figure 301 (SEQ ID NO:301), Figure 303 (SEQ ID NO:303), Figure 305 (SEQ ID NO:305), Figure 307 (SEQ ID NO:307), Figure 309 (SEQ ID NO:309), Figures 311A-311B (SEQ ID NO:311), Figure 313 (SEQ ID NO:313), Figure 315 (SEQ ID NO:315), Figure 317 (SEQ ID NO:317), Figure 319 (SEQ ID NO:319), Figure 321 (SEQ ID NO:321), Figure 323 (SEQ ID NO:323), Figure 325 (SEQ ID NO:325), Figure 327 (SEQ ID NO:327), Figure 329 (SEQ ID NO:329), Figure 331 (SEQ ID NO:331), Figure 333 (SEQ ID NO:333), Figure 335 (SEQ ID NO:335), Figure 337 (SEQ ID NO:337), Figure 339 (SEQ ID NO:339), Figure 341 (SEQ ID NO:341), Figure 343 (SEQ ID NO:343), Figure 345 (SEQ ID NO:345), Figure 347 (SEQ ID NO:347), Figure 349 (SEQ ID NO:349), Figures 351A-351B (SEQ ID NO:351), Figure 353 (SEQ ID NO:353), Figure 355 (SEQ ID NO:355), Figure 357 (SEQ ID NO:357), Figure 359 (SEQ ID NO:359), Figure 361 (SEQ ID NO:361), Figure 363 (SEQ ID NO:363), Figure 365 (SEQ ID NO:365), Figure 367 (SEQ ID NO:367), Figure 369 (SEQ ID NO:369), Figure 371 (SEQ ID NO:371) and Figure 373 (SEQ ID NO:373).

4. An isolated nucleic acid molecule having at least 80% nucleic acid sequence identity to the full-length coding sequence of the DNA deposited under any ATCC accession number shown in Table 7.

5. A vector comprising the nucleic acid of Claim 1.

6. A host cell comprising the vector of Claim 5.

7. The host cell of Claim 6, wherein said cell is a CHO cell.

8. The host cell of Claim 6, wherein said cell is an *E. coli*.

9. The host cell of Claim 6, wherein said cell is a yeast cell.

10. A process for producing a PRO polypeptide comprising culturing the host cell of Claim 6 under conditions suitable for expression of said PRO polypeptide and recovering said PRO polypeptide from the cell culture.

11. An isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID

NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) and Figure 374 (SEQ ID NO:374).

12. An isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence encoded by the full-length coding sequence of the DNA deposited under any ATCC accession number shown in Table 7.

13. A chimeric molecule comprising a polypeptide according to Claim 11 fused to a heterologous amino acid sequence.

14. The chimeric molecule of Claim 13, wherein said heterologous amino acid sequence is an epitope tag sequence.

15. The chimeric molecule of Claim 13, wherein said heterologous amino acid sequence is a Fc region of an immunoglobulin.

16. An antibody which specifically binds to a polypeptide according to Claim 11.

17. The antibody of Claim 16, wherein said antibody is a monoclonal antibody, a humanized antibody or a single-chain antibody.

18. An isolated nucleic acid molecule having at least 80% nucleic acid sequence identity to:

(a) a nucleotide sequence encoding the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID

NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), lacking its associated signal peptide;

(b) a nucleotide sequence encoding an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure

144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), with its associated signal peptide; or

(c) a nucleotide sequence encoding an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18

(SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure

284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), lacking its associated signal peptide.

19. An isolated polypeptide having at least 80% amino acid sequence identity to:

(a) an amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID

NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), lacking its associated signal peptide;

(b) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26

(SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure

292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), with its associated signal peptide; or

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID

NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), lacking its associated signal peptide.

20. A method for treating a cardiovascular, endothelial or angiogenic disorder in a mammal comprising administering to the mammal a therapeutically effective amount of a polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32),

Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure 256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure

298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), or agonist or antagonist thereof.

21. The method according to Claim 20, wherein the mammal is human.

22. The method of Claim 21, wherein the human has suffered myocardial infarction.

23. The method of Claim 21, wherein the human has cardiac hypertrophy, trauma, a cancer, or age-related macular degeneration.

24. The method of Claim 23, wherein the cardiac hypertrophy is characterized by the presence of an elevated level of $PGF_{2\alpha}$.

25. The method of Claim 20, wherein the polypeptide is administered together with a cardiovascular, endothelial or angiogenic agent.

26. The method of Claim 23, wherein the polypeptide is administered following primary angioplasty.

27. The method of Claim 20, wherein the cardiovascular, endothelial or angiogenic disorder is cancer.

28. The method of Claim 27, wherein the polypeptide is administered in combination with a chemotherapeutic agent, a growth inhibitory agent or a cytotoxic agent.

29. The method of Claim 20, wherein said agonist is an antibody to said polypeptide.

30. The method of Claim 20, wherein said antagonist is an antibody to said polypeptide.

31. A method for treating a cardiovascular, endothelial or angiogenic disorder in a mammal comprising administering to the mammal a nucleic acid molecule that encodes a polypeptide shown in Figure 2 (SEQ ID NO:2), Figure 4 (SEQ ID NO:4), Figure 6 (SEQ ID NO:6), Figure 8 (SEQ ID NO:8), Figure 10 (SEQ ID NO:10), Figure 12 (SEQ ID NO:12), Figure 14 (SEQ ID NO:14), Figure 16 (SEQ ID NO:16), Figure 18 (SEQ ID NO:18), Figure 20 (SEQ ID NO:20), Figure 22 (SEQ ID NO:22), Figure 24 (SEQ ID NO:24), Figure 26 (SEQ ID NO:26), Figure 28 (SEQ ID NO:28), Figure 30 (SEQ ID NO:30), Figure 32 (SEQ ID NO:32), Figure 34 (SEQ ID NO:34), Figure 36 (SEQ ID NO:36), Figure 38 (SEQ ID NO:38), Figure 40 (SEQ ID NO:40), Figure 42 (SEQ ID NO:42), Figure 44 (SEQ ID NO:44), Figure 46 (SEQ ID NO:46), Figure 48 (SEQ ID NO:48), Figure 50 (SEQ ID NO:50), Figure 52 (SEQ ID NO:52), Figure 54 (SEQ ID NO:54), Figure 56 (SEQ ID NO:56), Figure 58 (SEQ ID NO:58), Figure 60 (SEQ ID NO:60), Figure 62 (SEQ ID NO:62), Figure 64 (SEQ ID NO:64), Figure 66 (SEQ ID NO:66), Figure 68 (SEQ ID NO:68), Figure 70 (SEQ ID NO:70), Figure 72 (SEQ ID NO:72), Figure 74 (SEQ ID NO:74), Figure 76 (SEQ ID NO:76), Figure 78 (SEQ ID NO:78), Figure 80 (SEQ ID NO:80), Figure 82 (SEQ ID NO:82), Figure 84 (SEQ ID NO:84), Figure 86 (SEQ ID NO:86), Figure 88 (SEQ ID NO:88), Figure 90 (SEQ ID NO:90), Figure 92 (SEQ ID NO:92), Figure 94 (SEQ ID NO:94), Figure 96 (SEQ ID NO:96), Figure 98 (SEQ ID NO:98), Figure 100 (SEQ ID NO:100), Figure 102 (SEQ ID NO:102), Figure 104 (SEQ ID NO:104), Figure 106 (SEQ ID NO:106), Figure 108 (SEQ ID NO:108), Figure 110 (SEQ ID NO:110), Figure 112 (SEQ ID NO:112), Figure 114 (SEQ ID NO:114), Figure 116 (SEQ ID NO:116), Figure 118 (SEQ ID NO:118), Figure 120 (SEQ ID NO:120), Figure 122 (SEQ ID NO:122), Figure 124 (SEQ ID NO:124), Figure 126 (SEQ ID NO:126), Figure 128 (SEQ ID NO:128), Figure 130 (SEQ ID NO:130), Figure 132 (SEQ ID NO:132), Figure 134 (SEQ ID NO:134), Figure 136 (SEQ ID NO:136), Figure 138 (SEQ ID NO:138), Figure 140 (SEQ ID NO:140), Figure 142 (SEQ ID NO:142), Figure 144 (SEQ ID NO:144), Figure 146 (SEQ ID NO:146), Figure 148 (SEQ ID NO:148), Figure 150 (SEQ ID NO:150), Figure 152 (SEQ ID NO:152), Figure 154 (SEQ ID NO:154), Figure 156 (SEQ ID NO:156), Figure 158 (SEQ ID NO:158), Figure 160 (SEQ ID NO:160), Figure 162 (SEQ ID NO:162), Figure 164 (SEQ ID NO:164), Figure 166 (SEQ ID NO:166), Figure 168 (SEQ ID NO:168), Figure 170 (SEQ ID NO:170), Figure 172 (SEQ ID NO:172), Figure 174 (SEQ ID NO:174), Figure 176 (SEQ ID NO:176), Figure 178 (SEQ ID NO:178), Figure 180 (SEQ ID NO:180), Figure 182 (SEQ ID NO:182), Figure 184 (SEQ ID NO:184), Figure 186 (SEQ ID NO:186), Figure 188 (SEQ ID NO:188), Figure 190 (SEQ ID NO:190), Figure 192 (SEQ ID NO:192), Figure 194 (SEQ ID NO:194), Figure 196 (SEQ ID NO:196), Figure 198 (SEQ ID NO:198), Figure 200 (SEQ ID NO:200), Figure 202 (SEQ ID NO:202), Figure 204 (SEQ ID NO:204), Figure 206 (SEQ ID NO:206), Figure 208 (SEQ ID NO:208), Figure 210 (SEQ ID NO:210), Figure 212 (SEQ ID NO:212), Figure 214 (SEQ ID NO:214), Figure 216 (SEQ ID NO:216), Figure 218 (SEQ ID NO:218), Figure 220 (SEQ ID NO:220), Figure 222 (SEQ ID NO:222), Figure 224 (SEQ ID NO:224), Figure 226 (SEQ ID NO:226), Figure 228 (SEQ ID NO:228), Figure 230 (SEQ ID NO:230), Figure 232 (SEQ ID NO:232), Figure 234 (SEQ ID NO:234), Figure 236 (SEQ ID NO:236), Figure 238 (SEQ ID NO:238), Figure 240 (SEQ ID NO:240), Figure 242 (SEQ ID NO:242), Figure 244 (SEQ ID NO:244), Figure 246 (SEQ ID NO:246), Figure 248 (SEQ ID NO:248), Figure 250 (SEQ ID NO:250), Figure 252 (SEQ ID NO:252), Figure 254 (SEQ ID NO:254), Figure

256 (SEQ ID NO:256), Figure 258 (SEQ ID NO:258), Figure 260 (SEQ ID NO:260), Figure 262 (SEQ ID NO:262), Figure 264 (SEQ ID NO:264), Figure 266 (SEQ ID NO:266), Figure 268 (SEQ ID NO:268), Figure 270 (SEQ ID NO:270), Figure 272 (SEQ ID NO:272), Figure 274 (SEQ ID NO:274), Figure 276 (SEQ ID NO:276), Figure 278 (SEQ ID NO:278), Figure 280 (SEQ ID NO:280), Figure 282 (SEQ ID NO:282), Figure 284 (SEQ ID NO:284), Figure 286 (SEQ ID NO:286), Figure 288 (SEQ ID NO:288), Figure 290 (SEQ ID NO:290), Figure 292 (SEQ ID NO:292), Figure 294 (SEQ ID NO:294), Figure 296 (SEQ ID NO:296), Figure 298 (SEQ ID NO:298), Figure 300 (SEQ ID NO:300), Figure 302 (SEQ ID NO:302), Figure 304 (SEQ ID NO:304), Figure 306 (SEQ ID NO:306), Figure 308 (SEQ ID NO:308), Figure 310 (SEQ ID NO:310), Figure 312 (SEQ ID NO:312), Figure 314 (SEQ ID NO:314), Figure 316 (SEQ ID NO:316), Figure 318 (SEQ ID NO:318), Figure 320 (SEQ ID NO:320), Figure 322 (SEQ ID NO:322), Figure 324 (SEQ ID NO:324), Figure 326 (SEQ ID NO:326), Figure 328 (SEQ ID NO:328), Figure 330 (SEQ ID NO:330), Figure 332 (SEQ ID NO:332), Figure 334 (SEQ ID NO:334), Figure 336 (SEQ ID NO:336), Figure 338 (SEQ ID NO:338), Figure 340 (SEQ ID NO:340), Figure 342 (SEQ ID NO:342), Figure 344 (SEQ ID NO:344), Figure 346 (SEQ ID NO:346), Figure 348 (SEQ ID NO:348), Figure 350 (SEQ ID NO:350), Figure 352 (SEQ ID NO:352), Figure 354 (SEQ ID NO:354), Figure 356 (SEQ ID NO:356), Figure 358 (SEQ ID NO:358), Figure 360 (SEQ ID NO:360), Figure 362 (SEQ ID NO:362), Figure 364 (SEQ ID NO:364), Figure 366 (SEQ ID NO:366), Figure 368 (SEQ ID NO:368), Figure 370 (SEQ ID NO:370), Figure 372 (SEQ ID NO:372) or Figure 374 (SEQ ID NO:374), or agonist or antagonist thereof.

32. The method of Claim 31, wherein said agonist is an antibody to said polypeptide.

33. The method of Claim 31, wherein said antagonist is an antibody to said polypeptide.

34. The method of Claim 31, wherein the mammal is human.

35. The method of Claim 31, wherein the nucleic acid molecule is administered via *ex vivo* gene therapy.

36. A method for inhibiting endothelial cell growth in a mammal comprising administering to the mammal a PRO247, PRO720 or PRO4302 polypeptide or agonist thereof, wherein endothelial cell growth in said mammal is inhibited.

37. A method for stimulating endothelial cell growth in a mammal comprising administering to the mammal a PRO21, PRO181, PRO205, PRO214, PRO221, PRO229, PRO231, PRO238, PRO241, PRO247, PRO256, PRO258, PRO263, PRO265, PRO295, PRO321, PRO322, PRO337, PRO363, PRO365, PRO444, PRO533, PRO697, PRO725, PRO771, PRO788, PRO791, PRO819, PRO827, PRO828, PRO836, PRO846, PRO865, PRO1005, PRO1006, PRO1007, PRO1025, PRO1029, PRO1054, PRO1071, PRO1075, PRO1079,

PRO1080, PRO1114, PRO1131, PRO1155, PRO1160, PRO1184, PRO1186, PRO1190, PRO1192, PRO1195, PRO1244, PRO1272, PRO1273, PRO1274, PRO1279, PRO1283, PRO1286, PRO1306, PRO1309, PRO1325, PRO1329, PRO1347, PRO1356, PRO1376, PRO1382, PRO1411, PRO1412, PRO1419, PRO1474, PRO1477, PRO1488, PRO1508, PRO1550, PRO1556, PRO1760, PRO1782, PRO1787, PRO1801, PRO1868, PRO1887, PRO1890, PRO3438, PRO3444, PRO4302, PRO4324, PRO4333, PRO4341, PRO4342, PRO4353, PRO4354, PRO4356, PRO4371, PRO4405, PRO4408, PRO4422, PRO4425, PRO4499, PRO5723, PRO5725, PRO5737, PRO5776, PRO6006, PRO6029, PRO6071, PRO7436, PRO9771, PRO9821, PRO9873, PRO10008, PRO10096, PRO19670, PRO20040, PRO20044, PRO21055, PRO21384 or PRO28631 polypeptide, or agonist thereof, wherein endothelial cell growth in said mammal is stimulated.

38. A method for inducing cardiac hypertrophy in a mammal comprising administering to the mammal a PRO21 polypeptide or agonist thereof, wherein cardiac hypertrophy in said mammal is induced.

39. A method for stimulating angiogenesis induced by a PRO1376 or PRO1449 polypeptide in a mammal comprising administering a therapeutically effective amount of said polypeptide to the mammal, wherein said angiogenesis is stimulated.

40. A method for inducing endothelial cell apoptosis comprising administering to the endothelial cell a PRO4302 polypeptide or agonist thereof, wherein apoptosis in said endothelial cell is induced.

41. A method for stimulating smooth muscle cell growth comprising administering to the smooth muscle cell a PRO162, PRO181, PRO182, PRO195, PRO204, PRO221, PRO230, PRO256, PRO258, PRO533, PRO697, PRO725, PRO738, PRO826, PRO836, PRO840, PRO846, PRO865, PRO982, PRO1025, PRO1029, PRO1071, PRO1080, PRO1083, PRO1134, PRO1160, PRO1182, PRO1184, PRO1186, PRO1192, PRO1265, PRO1274, PRO1279, PRO1283, PRO1306, PRO1308, PRO1309, PRO1325, PRO1337, PRO1338, PRO1343, PRO1376, PRO1387, PRO1411, PRO1412, PRO1415, PRO1434, PRO1474, PRO1488, PRO1550, PRO1556, PRO1567, PRO1600, PRO1754, PRO1758, PRO1760, PRO1787, PRO1865, PRO1868, PRO1917, PRO1928, PRO3438, PRO3562, PRO4302, PRO4333, PRO4345, PRO4353, PRO4354, PRO4405, PRO4408, PRO4430, PRO4503, PRO5725, PRO6714, PRO9771, PRO9820, PRO9940, PRO10096, PRO21055, PRO21184 or PRO21366 polypeptide, or agonist thereof, wherein smooth muscle cell growth in said smooth muscle cell is stimulated.

42. A method for inducing endothelial cell tube formation comprising administering to the endothelial cell a PRO178, PRO195, PRO228, PRO301, PRO302, PRO532, PRO724, PRO730, PRO734, PRO793, PRO871, PRO938, PRO1012, PRO1120, PRO1139, PRO1198, PRO1287, PRO1361, PRO1864, PRO1873, PRO2010, PRO3579, PRO4313, PRO4527, PRO4538, PRO4553, PRO4995, PRO5730, PRO6008, PRO7223, PRO7248 or PRO7261 polypeptide, or agonist thereof, wherein tube formation in said endothelial cell is induced.

FIGURE 1

GCCCACGCGTCCG<u>ATG</u>GCGTTCACGTTCGCGGCCTTCTGCTACATGCTGGCGCTGCTGCT
CACTGCCGCGCTCATCTTCTTCGCCATTTGGCACATTATAGCATTTGATGAGCTGAAGAC
TGATTACAAGAATCCTATAGACCAGTGTAATACCCTGAATCCCCTTGTACTCCCAGAGTA
CCTCATCCACGCTTTCTTCTGTGTCATGTTTCTTTGTGCAGCAGAGTGGCTTACACTGGG
TCTCAATATGCCCCTCTTGGCATATCATATTTGGAGGTATATGAGTAGACCAGTGATGAG
TGGCCCAGGACTCTATGACCCTACAACCATCATGAATGCAGATATTCTAGCATATTGTCA
GAAGGAAGGATGGTGCAAATTAGCTTTTTATCTTCTAGCATTTTTTTACTACCTATATGG
CATGATCTATGTTTTGGTGAGCTCT<u>TAG</u>AACAACACACAGAAGAATTGGTCCAGTTAAGT
GCATGCAAAAAGCCACCAAATGAAGGGATTCTATCCAGCAAGATCCTGTCCAAGAGTAGC
CTGTGGAATCTGATCAGTTACTTTAAAAAATGACTCCTTATTTTTTAAATGTTTCCACAT
TTTTGCTTGTGGAAAGACTGTTTTCATATGTTATACTCAGATAAAGATTTTAAATGGTAT
TACGTATAAATTAATATAAAATGATTACCTCTGGTGTTGACAGGTTTGAACTTGCACTTC
TTAAGGAACAGCCATAATCCTCTGAATGATGCATTAATTACTGACTGTCCTAGTACATTG
GAAGCTTTTGTTTATAGGAACTTGTAGGGCTCATTTTGGTTTCATTGAAACAGTATCTAA
TTATAAATTAGCTGTAGATATCAGGTGCTTCTGATGAAGTGAAAATGTATATCTGACTAG
TGGGAAACTTCATGGGTTTCCTCATCTGTCATGTCGATGATTATATATGGATACATTTAC
AAAAATAAAAAGCGGGAATTTTCCCTTCGCTTGAATATTATCCCTGTATATTGCATGAAT
GAGAGATTTCCCATATTTCCATCAGAGTAATAAATATACTTGCTTTAATTCTTAAGCATA
AGTAAACATGATATAAAAATATATGCTGAATTACTTGTGAAGAATGCATTTAAAGCTATT
TTAAATGTGTTTTTATTTGTAAGACATTACTTATTAAGAAATTGGTTATTATGCTTACTG
TTCTAATCTGGTGGTAAAGGTATTCTTAAGAATTTGCAGGTACTACAGATTTTCAAAACT
GAATGAGAGAAAATTGTATAACCATCCTGCTGTTCCTTTAGTGCAATACAATAAAACTCT
GAAATTAAGACTC

FIGURE 2

MAFTFAAFCYMLALLLTAALIFFAIWHIIAFDELKTDYKNPIDQCNTLNPLVLPEYLIHA
FFCVMFLCAAEWLTLGLNMPLLAYHIWRYMSRPVMSGPGLYDPTTIMNADILAYCQKEGW
CKLAFYLLAFFYYLYGMIYVLVSS

Important features:
Signal peptide:
amino acids 1-20

Type II transmembrane domain:
amino acids 11-31

Other transmembrane domain:
amino acids 57-77 and 123-143

FIGURE 3

GGCTCAGAGGCCCCACTGGACCCTCGGCTCTTCCTTGGACTTCTTGTGTGTTCTGTGAGC
TTCGCTGGATTCAGGGTCTTGGGCATCAGAGGTGAGAGGGTGGGAAGGTCCGCCGCG**ATG**
GGGAAGCCCTGGCTGCGTGCGCTACAGCTGCTGCTCCTGCTGGGCGCGTCGTGGGCGCGG
GCGGGCGCCCCGCGCTGCACCTACACCTTCGTGCTGCCCCCGCAGAAGTTCACGGGCGCT
GTGTGCTGGAGCGGCCCCGCATCCACGCGGGCGACGCCCGAGGCCGCCAACGCCAGCGAG
CTGGCGGCGCTGCGCATGCGCGTCGGCCGCCACGAGGAGCTGTTACGCGAGCTGCAGAGG
CTGGCGGCGGCCGACGGCGCCGTGGCCGGCGAGGTGCGCGCGCTGCGCAAGGAGAGCCGC
GGCCTGAGCGCGCGCCTGGGCCAGTTGCGCGCGCAGCTGCAGCACGAGGCGGGGCCCGGG
GCGGGCCCGGGGGCGGATCTGGGGGCGGAGCCTGCCGCGGCGCTGGCGCTGCTCGGGGAG
CGCGTGCTCAACGCGTCCGCCGAGGCTCAGCGCGCAGCCGCCCGGTTCCACCAGCTGGAC
GTCAAGTTCCGCGAGCTGGCGCAGCTCGTCACCCAGCAGAGCAGTCTCATCGCCCGCCTG
GAGCGCCTGTGCCCGGGAGGCGCGGGCGGGCAGCAGCAGGTCCTGCCGCCACCCCCACTG
GTGCCTGTGGTTCCGGTCCGTCTTGTGGGTAGCACCAGTGACACCAGTAGGATGCTGGAC
CCAGCCCCAGAGCCCCAGAGAGACCAGACCCAGAGACAGCAGGAGCCCATGGCTTCTCCC
ATGCCTGCAGGTCACCCTGCGGTCCCCACCAAGCCTGTGGGCCCGTGGCAGGATTGTGCA
GAGGCCCGCCAGGCAGGCCATGAACAGAGTGGAGTGTATGAACTGCGAGTGGGCCGTCAC
GTAGTGTCAGTATGGTGTGAGCAGCAACTGGAGGGTGGAGGCTGGACTGTGATCCAGCGG
AGGCAAGATGGTTCAGTCAACTTCTTCACTACCTGGCAGCACTATAAGGCGGGCTTTGGG
CGGCCAGACGGAGAATACTGGCTGGGCCTTGAACCCGTGTATCAGCTGACCAGCCGTGGG
GACCATGAGCTGCTGGTTCTCCTGGAGGACTGGGGGGCCGTGGAGCACGTGCCCACTAT
GATGGCTTCTCCCTGGAACCCGAGAGCGACCACTACCGCCTGCGGCTTGGCCAGTACCAT
GGTGATGCTGGAGACTCTCTTTCCTGGCACAATGACAAGCCCTTCAGCACCGTGGATAGG
GACCGAGACTCCTATTCTGGTAACTGTGCCCTGTACCAGCGGGGAGGCTGGTGGTACCAT
GCCTGTGCCCACTCCAACCTCAACGGTGTGTGGCACCACGGCGGCCACTACCGAAGCCGC
TACCAGGATGGTGTCTACTGGGCTGAGTTTCGTGGTGGGGCATATTCTCTCAGGAAGGCC
GCCATGCTCATTCGGCCCCTGAAGCTG**TGA**CTCTGTGTTCCTCTGTCCCCTAGGCCCTAG
AGGACATTGGTCAGCAGGAGCCCAAGTTGTTCTGGCCACACCTTCTTTGTGGCTCAGTGC
CAATGTGTCCCACAGAACTTCCCACTGTGGATCTGTGACCCTGGGCGCTGAAAATGGGAC
CCAGGAATCCCCCCCGTCAATATCTTGGCCTCAGATGGCTCCCCAAGGTCATTCATATCT
CGGTTTGAGCTCATATCTTATAATAACACAAAGTAGCCAC

FIGURE 4

MGKPWLRALQLLLLLGASWARAGAPRCTYTFVLPPQKFTGAVCWSGPASTRATPEAANAS
ELAALRMRVGRHEELLRELQRLAAADGAVAGEVRALRKESRGLSARLGQLRAQLQHEAGP
GAGPGADLGAEPAAALALLGERVLNASAEAQRAAARFHQLDVKFRELAQLVTQQSSLIAR
LERLCPGGAGGQQQVLPPPPLVPVVPVRLVGSTSDTSRMLDPAPEPQRDQTQRQQEPMAS
PMPAGHPAVPTKPVGPWQDCAEARQAGHEQSGVYELRVGRHVVSVWCEQQLEGGGWTVIQ
RRQDGSVNFFTTWQHYKAGFGRPDGEYWLGLEPVYQLTSRGDHELLVLLEDWGGRGARAH
YDGFSLEPESDHYRLRLGQYHGDAGDSLSWHNDKPFSTVDRDRDSYSGNCALYQRGGWWY
HACAHSNLNGVWHHGGHYRSRYQDGVYWAEFRGGAYSLRKAAMLIRPLKL

Signal peptide:
Amino acids 1-20

N-glycosylation sites:
Amino acids 58-62;145-149

cAMP- and cGMP-dependent protein kinase phosphorylation site:
Amino acids 97-101

Tyrosine kinase phosphorylation site:
Amino acids 441-448

N-myristoylation sites:
Amino acids
16-22;23-29;87-93;108-114;121-127;125-131;129-135;187-193;293-299;353-359;378-384;445-451;453-459

Cell attachment sequence:
Amino acids 340-343

Fibrinogen beta and gamma chains C-terminal domain signature:
Amino acids 418-431

FIGURE 5

CCCACGCGTCCGGCGCCGTGGCCTCGCGTCCATCTTTGCCGTTCTCTCGGACCTGTCACA
AAGGAGTCGCGCCGCCGCCGCCGCCCCCTCCCTCCGGTGGGCCCGGGAGGTAGAGAAAGT
CAGTGCCACAGCCCGACCGCGCTGCTCTGAGCCCTGGGCACGCGGAACGGGAGGGAGTCT
GAGGGTTGGGGACGTCTGTGAGGGAGGGGAACAGCCGCTCGAGCCTGGGGCGGGCGGACC
GGACTGGGGCCGGGGTAGGCTCTGGAAAGGGCCCGGGAGAGAGGTGGCGTTGGTCAGAAC
CTGAGAAACAGCCGAGAGGTTTTCCACCGAGGCCCGCGCTTGAGGGATCTGAAGAGGTTC
CTAGAAGAGGGTGTTCCCTCTTTCGGGGGTCCTCACCAGAAGAGGTTCTTGGGGGTCGCC
CTTCTGAGGAGGCTGCGGCTAACAGGGCCCAGAACTGCCATTGGATGTCCAGAATCCCCT
GTAGTTGATAATGTTGGGAATAAGCTCTGCAACTTTCTTTGGCATTCAGTTGTTAAAAAC
AAATAGGATGCAAATTCCTCAACTCCAGGTTATGAAAACAGTACTTGGAAAACTGAAAAC
TACCTAA**ATG**ATCGTCTTTGGTTGGGCCGTGTTCTTAGCGAGCAGAAGCCTTGGCCAGGG
TCTGTTGTTGACTCTCGAAGAGCACATAGCCCACTTCCTAGGGACTGGAGGTGCCGCTAC
TACCATGGGTAATTCCTGTATCTGCCGAGATGACAGTGGAACAGATGACAGTGTTGACAC
CCAACAGCAACAGGCCGAGAACAGTGCAGTACCCACTGCTGACACAAGGAGCCAACCACG
GGACCCTGTTCGGCCACCAAGGAGGGGCCGAGGACCTCATGAGCCAAGGAGAAAGAAACA
AAATGTGGATGGGCTAGTGTTGGACACACTGGCAGTAATACGGACTCTTGTAGATAAG**TA**
AGTATCTGACTCACGGTCACCTCCAGTGGAATGAAAAGTGTTCTGCCCGGAACCATGACT
TTAGGACTCCTTCAGTTCCTTTAGGACATACTCGCCAAGCCTTGTGCTCACAGGGCAAAG
GAGAATATTTTAATGCTCCGCTGATGGCAGAGTAAATGATAAGATTTGATGTTTTTGCTT
GCTGTCATCTACTTTGTCTGGAAATGTCTAAATGTTTCTGTAGCAGAAAACACGATAAAG
CTATGATCTTTATTAGAG

FIGURE 6

MIVFGWAVFLASRSLGQGLLLTLEEHIAHFLGTGGAATTMGNSCICRDDSGTDDSVDTQQ
QQAENSAVPTADTRSQPRDPVRPPRRGRGPHEPRRKKQNVDGLVLDTLAVIRTLVDKO

Signal peptide:
amino acids 1-16

Casein kinase II phosphorylation site:
amino acids 22-26, 50-54, 113-117

N-myristoylation site:
amino acids 18-24, 32-38, 34-40, 35-41, 51-57

FIGURE 7

CGGACGCGTGGGGGAAACCCTTCCGAGAAAACAGCAACAAGCTGAGCTGCTGTGACAGAG
GGGAACAAG**ATG**GCGGCGCCGAAGGGGAGCCTCTGGGTGAGGACCCAACTGGGGCTCCCG
CCGCTGCTGCTGCTGACCATGGCCTTGGCCGGAGGTTCGGGGACCGCTTCGGCTGAAGCA
TTTGACTCGGTCTTGGGTGATACGGCGTCTTGCCACCGGGCCTGTCAGTTGACCTACCCC
TTGCACACCTACCCTAAGGAAGAGGAGTTGTACGCATGTCAGAGAGGTTGCAGGCTGTTT
TCAATTTGTCAGTTTGTGGATGATGGAATTGACTTAAATCGAACTAAATTGGAATGTGAA
TCTGCATGTACAGAAGCATATTCCCAATCTGATGAGCAATATGCTTGCCATCTTGGTTGC
CAGAATCAGCTGCCATTCGCTGAACTGAGACAAGAACAACTTATGTCCCTGATGCCAAAA
ATGCACCTACTCTTTCCTCTAACTCTGGTGAGGTCATTCTGGAGTGACATGATGGACTCC
GCACAGAGCTTCATAACCTCTTCATGGACTTTTTATCTTCAAGCCGATGACGGAAAAATA
GTTATATTCCAGTCTAAGCCAGAAATCCAGTACGCACCACATTTGGAGCAGGAGCCTACA
AATTTGAGAGAATCATCTCTAAGCAAAATGTCCTATCTGCAAATGAGAAATTCACAAGCG
CACAGGAATTTTCTTGAAGATGGAGAAAGTGATGGCTTTTTAAGATGCCTCTCTCTTAAC
TCTGGGTGGATTTTAACTACAACTCTTGTCCTCTCGGTGATGGTATTGCTTTGGATTTGT
TGTGCAACTGTTGCTACAGCTGTGGAGCAGTATGTTCCCTCTGAGAAGCTGAGTATCTAT
GGTGACTTGGAGTTTATGAATGAACAAAAGCTAAACAGATATCCAGCTTCTTCTCTTGTG
GTTGTTAGATCTAAAACTGAAGATCATGAAGAAGCAGGGCCTCTACCTACAAAAGTGAAT
CTTGCTCATTCTGAAAT**TTA**AGCATTTTTCTTTTAAAAGACAAGTGTAATAGACATCTAA
AATTCCACTCCTCATAGAGCTTTTAAAATGGTTTCATTGGATATAGGCCTTAAGAAATCA
CTATAAAATGCAAATAAAGTTACTCAAATCTGTG

FIGURE 8

MAAPKGSLWVRTQLGLPPLLLLTMALAGGSGTASAEAFDSVLGDTASCHRACQLTYPLHT
YPKEEELYACQRGCRLFSICQFVDDGIDLNRTKLECESACTEAYSQSDEQYACHLGCQNQ
LPFAELRQEQLMSLMPKMHLLFPLTLVRSFWSDMMDSAQSFITSSWTFYLQADDGKIVIF
QSKPEIQYAPHLEQEPTNLRESSLSKMSYLQMRNSQAHRNFLEDGESDGFLRCLSLNSGW
ILTTTLVLSVMVLLWICCATVATAVEQYVPSEKLSIYGDLEFMNEQKLNRYPASSLVVVR
SKTEDHEEAGPLPTKVNLAHSEI

Important features:
Signal peptide:
amino acids 1-31

Transmembrane domain:
amino acids 241-260

N-glycosylation site:
amino acids 90-93

FIGURE 9

TATTTACCATATCAGATTCACATTCAGTCCTCAGCAAA**ATG**AAGGGCTCCATTTTCACTC
TGTTTTTATTCTCTGTCCTATTTGCCATCTCAGAAGTGCGGAGCAAGGAGTCTGTGAGAC
TCTGTGGGCTAGAATACATACGGACAGTCATCTATATCTGTGCTAGCTCCAGGTGGAGAA
GGCATCTGGAGGGGATCCCTCAAGCTCAGCAAGCTGAGACAGGAAACTCCTTCCAGCTCC
CACATAAACGTGAGTTTTCTGAGGAAAATCCAGCGCAAAACCTTCCGAAGGTGGATGCCT
CAGGGGAAGACCGTCTTTGGGGTGGACAGATGCCCACTGAAGAGCTTTGGAAGTCAAAGA
AGCATTCAGTGATGTCAAGACAAGATTTACAAACTTTGTGTTGCACTGATGGCTGTTCCA
TGACTGATTTGAGTGCTCTTTGC**TAA**GACAAGAGCAAATACCCAATGGGTGGCAGAGCTT
TATCACATGTTTAATTACAGTGTTTTACTGCCTGGTAGAACACTAATATTGTGTTATTAA
AATGATGGCTTTTGGGTAGGCAAAACTTCTTTTCTAAAAGGTATAGCTGAGCGGTTGAAA
CCACAGTGATCTCTATTTTCTCCCTTTGCCAAGGTTAATGAACTGTTCTTTTCAAATTCT
ACTAATGCTTTGAAATTTCAAATGCTGCGCAAAATTGCAATAAAAATGCTATAAA

FIGURE 10

MKGSIFTLFLFSVLFAISEVRSKESVRLCGLEYIRTVIYICASSRWRRHLEGIPQAQQAE
TGNSFQLPHKREFSEENPAQNLPKVDASGEDRLWGGQMPTEELWKSKKHSVMSRQDLQTL
CCTDGCSMTDLSALC

Important features:
Signal sequence:
amino acids 1-18

cAMP- and cGMP-dependent protein kinase phosphorylation site:
amino acids 107-111

N-myristoylation sites:
amino acids 3-9,52-58,96-102,125-131

Insulin family signature:
amino acids 121-136

Insulin family proteins:
amino acids 28-46

FIGURE 11

CCCACGCGTCCGGACAAACTGGAGGTGAAAGGAGCTGGTACTGTCCACTGTGCTGTCGGT
GCTGAACCTGAGACGCGAGCGGACCAGTTGCTCCAGCACCTGAAGGCAACGCCCTCTTGC
ACCCTCTGTGCCCTGTGGGACCCGCTTCACCAACAGGACCCATATCAACTTGACAAAGGA
GTGTGGTATCGGACGTGGGAGAGAGTCCTCTGTTTGCCACCTGGGCGCTCATTCAGGCGT
GACTTTGGAGATTTCTATAGTTTTAGACCAAACTATTTTTTTTTCCCCAGCTAAGACGAT
CTTTTGAGAGTTTTTTTTTTTATTGTGATTTATATTTCCACAGCGTTTAGGAATCTTTCT
GGGGGACTTTTGTGACTGTTAAAATAAGGTGAAAAGCAATAAGG<u>**ATG**</u>TTTAAGTGCTGGT
CAGTTGTCTTGGTTCTCGGATTCATTTTTCTGGAGTCGGAAGGAAGGCCAACCAAAGAAG
GAGGATATGGCCTTAAATCCTATCAGCCTCTAATGAGATTGCGACATAAGCAGGAAAAAA
ATCAAGAAAGTTCAAGAGTCAAAGGATTTATGATTCAGGATGGCCCTTTTGGATCTTGTG
AAAATAAGTACTGTGGTTTGGGAAGACACTGTGTTACCAGCAGAGAGACAGGGCAAGCAG
AATGTGCCTGTATGGACCTTTGCAAACGTCACTACAAACCTGTGTGTGGATCTGACGGAG
AATTCTATGAAAACCACTGTGAAGTGCACAGAGCTGCTTGCCTGAAAAAACAAAAGATTA
CCATTGTTCACAATGAAGACTGCTTCTTTAAAGGAGATAAGTGCAAGACTACTGAATACA
GCAAGATGAAAAATATGCTATTAGATTTACAAAATCAAAAATATATTATGCAAGAAAATG
AAAATCCTAATGGCGACGACATATCTCGGAAGAAGCTATTGGTGGATCAAATGTTTAAAT
ATTTTGATGCAGACAGTAATGGACTTGTAGATATTAATGAACTAACTCAGGTGATAAAAC
AGGAAGAACTTGGCAAGGATCTCTTTGATTGTACTTTGTATGTTCTATTGAAATATGATG
ATTTTAATGCTGACAAGCACCTGGCTCTTGAAGAATTTTATAGAGCATTCCAAGTGATCC
AGTTGAGTCTGCCAGAAGATCAGAAACTAAGCATCACTGCAGCAACTGTGGGACAAAGTG
CTGTTCTGAGCTGTGCCATTCAAGGAACCCTGAGACCTCCCATTATCTGGAAAAGGAACA
ATATTATTCTAAATAATTTAGATTTGGAAGACATCAATGACTTTGGAGATGATGGGTCCT
TGTATATTACTAAGGTTACCACAACTCACGTTGGCAATTACACCTGCTATGCAGATGGCT
ATGAACAAGTCTATCAGACTCACATCTTCCAAGTGAATGTTCCTCCAGTCATCC

FIGURE 12

MFKCWSVVLVLGFIFLESEGRPTKEGGYGLKSYQPLMRLRHKQEKNQESSRVKGFMIQDG
PFGSCENKYCGLGRHCVTSRETGQAECACMDLCKRHYKPVCGSDGEFYENHCEVHRAACL
KKQKITIVHNEDCFFKGDKCKTTEYSKMKNMLLDLQNQKYIMQENENPNGDDISRKKLLV
DQMFKYFDADSNGLVDINELTQVIKQEELGKDLFDCTLYVLLKYDDFNADKHLALEEFYR
AFQVIQLSLPEDQKLSITAATVGQSAVLSCAIQGTLRPPIIWKRNNIILNNLDLEDINDF
GDDGSLYITKVTTTHVGNYTCYADGYEQVYQTHIFQVNVPPVI

Signal sequence:
Amino acids 1-20

N-glycosylation site:
Amino acids 318-322

Tyrosine kinase phosphorylation sites:
Amino acids 21-29;211-220

N-myristoylation sites:
Amino acids 63-69;83-89;317-323

Prokaryotic membrane lipoprotein lipid attachment site:
Amino acids 260-271

FIGURE 13

TGCCGGGCTGCGGGGCGCCTTGACTCTCCCTCCACCCTGCCTCCTCGGGCTCCACTCGTC
TGCCCCTGGACTCCCGTCTCCTCCTGTCCTCCGGCTTCCCAGAGCTCCCTCCTTATGGCA
GCAGCTTCCCGCGTCTCCGGCGCAGCTTCTCAGCGGACGACCCTCTCGCTCCGGGGCTGA
GCCCAGTCCCTGGATGTTGCTGAAACTCTCGAGATCATGCGCGGGTTTGGCTGCTGCTTC
CCCGCCGGGTGCCACTGCCACCGCCGCCGCCTCTGCTGCCGCCGTCCGCGGGATGCTCAG
TAGCCCGCTGCCCGGCCCCCGCGATCCTGTGTTCCTCGGAAGCCGTTTGCTGCTGCAGAG
TTGCACGAACTAGTC**ATG**GTGCTGTGGGAGTCCCCGCGGCAGTGCAGCAGCTGGACACTT
TGCGAGGGCTTTTGCTGGCTGCTGCTGCTGCCCGTCATGCTACTCATCGTAGCCCGCCCG
GTGAAGCTCGCTGCTTTCCCTACCTCCTTAAGTGACTGCCAAACGCCCACCGGCTGGAAT
TGCTCTGGTTATGATGACAGAGAAAATGATCTCTTCCTCTGTGACACCAACACCTGTAAA
TTTGATGGGGAATGTTTAAGAATTGGAGACACTGTGACTTGCGTCTGTCAGTTCAAGTGC
AACAATGACTATGTGCCTGTGTGTGGCTCCAATGGGGAGAGCTACCAGAATGAGTGTTAC
CTGCGACAGGCTGCATGCAAACAGCAGAGTGAGATACTTGTGGTGTCAGAAGGATCATGT
GCCACAGATGCAGGATCAGGATCTGGAGATGGAGTCCATGAAGGCTCTGGAGAAACTAGT
CAAAAGGAGACATCCACCTGTGATATTTGCCAGTTTGGTGCAGAATGTGACGAAGATGCC
GAGGATGTCTGGTGTGTGTGTAATATTGACTGTTCTCAAACCAACTTCAATCCCCTCTGC
GCTTCTGATGGGAAATCTTATGATAATGCATGCCAAATCAAAGAAGCATCGTGTCAGAAA
CAGGAGAAAATTGAAGTCATGTCTTTGGGTCGATGTCAAGATAACACAACTACAACTACT
AAGTCTGAAGATGGGCATTATGCAAGAACAGATTATGCAGAGAATGCTAACAAATTAGAA
GAAAGTGCCAGAGAACACCACATACCTTGTCCGGAACATTACAATGGCTTCTGCATGCAT
GGGAAGTGTGAGCATTCTATCAATATGCAGGAGCCATCTTGCAGGTGTGATGCTGGTTAT
ACTGGACAACACTGTGAAAAAAAGGACTACAGTGTTCTATACGTTGTTCCCGGTCCTGTA
CGATTTCAGTATGTCTTAATCGCAGCTGTGATTGGAACAATTCAGATTGCTGTCATCTGT
GTGGTGGTCCTCTGCATCACAAGGAAATGCCCCAGAAGCAACAGAATTCACAGACAGAAG
CAAAATACAGGGCACTACAGTTCAGACAATACAACAAGAGCGTCCACGAGGTTAATC**TAA**
AGGGAGCATGTTTCACAGTGGCTGGACTACCGAGAGCTTGGACTACACAATACAGTATTA
TAGACAAAAGAATAAGACAAGAGATCTACACATGTTGCCTTGCATTTGTGGTAATCTACA
CCAATGAAAACATGTACTACAGCTATATTTGATTATGTATGGATATATTTGAAATAGTAT
ACATTGTCTTGATGTTTTTTCTGTAATGTAAATAAACTATTTATATCACACAATATAGTT
TTTTCTTTCCCATGTATTTGTTATATATAATAAATACTCAGTGATGAG

FIGURE 14

MVLWESPRQCSSWTLCEGFCWLLLLPVMLLIVARPVKLAAFPTSLSDCQTPTGWNCSGY
DDRENDLFLCDTNTCKFDGECLRIGDTVTCVCQFKCNNDYVPVCGSNGESYQNECYLRQ
AACKQQSEILVVSEGSCATDAGSGSGDGVHEGSGETSQKETSTCDICQFGAECDEDAED
VWCVCNIDCSQTNFNPLCASDGKSYDNACQIKEASCQKQEKIEVMSLGRCQDNTTTTTK
SEDGHYARTDYAENANKLEESAREHHIPCPEHYNGFCMHGKCEHSINMQEPSCRCDAGY
TGQHCEKKDYSVLYVVPGPVRFQYVLIAAVIGTIQIAVICVVVLCITRKCPRSNRIHRQ
KQNTGHYSSDNTTRASTRLI

FIGURE 15

GGAGCTCAGCCCAGTGGGCAGTCTGAAG<u>ATG</u>GCCAATTACACGCTGGCACCAGAGGATGA
ATATGATGTCCTCATAGAAGGTGAACTGGAGAGCGATGAGGCAGAGCAATGTGACAAGTA
TGACGCCCAGGCACTCTCAGCCCAGCTGGTGCCATCACTCTGCTCTGCTGTGTTTGTGAT
CGGTGTCCTGGACAATCTCCTGGTTGTGCTTATCCTGGTAAAATATAAAGGACTCAAACG
CGTGGAAAATATCTATCTTCTAAACTTGGCAGTTTCTAACTTGTGTTTCTTGCTTACCCT
GCCCTTCTGGGCTCATGCTGGGGGCGATCCCATGTGTAAAATTCTCATTGGACTGTACTT
CGTGGGCCTGTACAGTGAGACATTTTTCAATTGCCTTCTGACTGTGCAAAGGTACCTAGT
GTTTTTGCACAAGGGCAACTTTTTCTCAGCCAGGAGGAGGGTGCCCTGTGGCATCATTAC
AAGTGTCCTGGCATGGGTAACAGCCATTCTGGCCACTTTGCCTGAATACGTGGTTTATAA
ACCTCAGATGGAAGACCAGAAATACAAGTGTGCATTTAGCAGAACTCCCTTCCTGCCAGC
TGATGAGACATTCTGGAAGCATTTTCTGACTTTAAAAATGAACATTTCGGTTCTTGTCCT
CCCCCTATTTATTTTTACATTTCTCTATGTGCAAATGAGAAAAACACTAAGGTTCAGGGA
GCAGAGGTATAGCCTTTTCAAGCTTGTTTTTGCCATAATGGTAGTCTTCCTTCTGATGTG
GGCGCCCTACAATATTGCATTTTTCCTGTCCACTTTCAAAGAACACTTCTCCCTGAGTGA
CTGCAAGAGCAGCTACAATCTGGACAAAAGTGTTCACATCACTAAACTCATCGCCACCAC
CCACTGCTGCATCAACCCTCTCCTGTATGCGTTTCTTGATGGGACATTTAGCAAATACCT
CTGCCGCTGTTTCCATCTGCGTAGTAACACCCCACTTCAACCCAGGGGGCAGTCTGCACA
AGGCACATCGAGGGAAGAACCTGACCATTCCACCGAAGTG<u>TAA</u>ACTAGCATCCACCAAAT
GCAAGAAGAATAAACATGGATTTTCATCTTTCTGCATTATTTCATGTAAATTTTCTACAC
ATTTGTATACAAAATCGGATACAGGAAGAAAAGGGAGAGGTGAGCTAACATTTGCTAAGC
ACTGAATTTGTCTCAGGCACCGTGCAAGGCTCTTTACAAACGTGAGCTCCTTCGCCTCCT
ACCACTTGTCCATAGTGTGGATAGGACTAGTCTCATTTCTCTGAGAAGAAAACTAAGGCG
CGGAAATTTGTCTAAGATCACATAACTAGGAAGTGGCAGAACTGATTCTCCAGCCCTGGT
AGCATTTGCTCAGAGCCTACGCTTGGTCCAGAACATCAAACTCCAAACCCTGGGGACAAA
CGACATGAAATAAATGTATTTTAAAACATCTAAAA

FIGURE 16

MANYTLAPEDEYDVLIEGELESDEAEQCDKYDAQALSAQLVPSLCSAVFVIGVLDNLLVV
LILVKYKGLKRVENIYLLNLAVSNLCFLLTLPFWAHAGGDPMCKILIGLYFVGLYSETFF
NCLLTVQRYLVFLHKGNFFSARRRVPCGIITSVLAWVTAILATLPEYVVYKPQMEDQKYK
CAFSRTPFLPADETFWKHFLTLKMNISVLVLPLFIFTFLYVQMRKTLRFREQRYSLFKLV
FAIMVVFLLMWAPYNIAFFLSTFKEHFSLSDCKSSYNLDKSVHITKLIATTHCCINPLLY
AFLDGTFSKYLCRCFHLRSNTPLQPRGQSAQGTSREEPDHSTEV

Signal sequence:
None

Transmembrane domain:
41-61, 76-96, 109-129, 147-167, 199-219, 237-257, 285-305

7 transmembrane receptor (rhodopsin family):
55-300

N-glycosylation site:
3-6, 205-208

Tyrosine kinase phosphorylation site:
70-76, 171-179, 228-234

N-myristoylation site:
52-57, 136-141, 148-153

G-protein coupled receptors:
55-85, 96-136, 209-220, 235-254, 292-308

FIGURE 17

CGGACGCGTGGGCGGACGCGTGGGCGGCCCACGGCGCCCGCGGGCTGGGGCGGTCGCTTC
TTCCTTCTCCGTGGCCTACGAGGGTCCCCAGCCTGGGTAAAGATGGCCCCATGGCCCCCG
AAGGGCCTAGTCCCAGCTGTGCTCTGGGGCCTCAGCCTCTTCCTCAACCTCCCAGGACCT
ATCTGGCTCCAGCCCTCTCCACCTCCCCAGTCTTCTCCCCCGCCTCAGCCCCATCCGTGT
CATACCTGCCGGGGACTGGTTGACAGCTTTAACAAGGGCCTGGAGAGAACCATCCGGGAC
AACTTTGGAGGTGGAAACACTGCCTGGGAGGAAGAGAATTTGTCCAAATACAAAGACAGT
GAGACCCGCCTGGTAGAGGTGCTGGAGGGTGTGTGCAGCAAGTCAGACTTCGAGTGCCAC
CGCCTGCTGGAGCTGAGTGAGGAGCTGGTGGAGAGCTGGTGGTTTCACAAGCAGCAGGAG
GCCCCGGACCTCTTCCAGTGGCTGTGCTCAGATTCCCTGAAGCTCTGCTGCCCCGCAGGC
ACCTTCGGGCCCTCCTGCCTTCCCTGTCCTGGGGGAACAGAGAGGCCCTGCGGTGGCTAC
GGGCAGTGTGAAGGAGAAGGGACACGAGGGGGCAGCGGGCACTGTGACTGCCAAGCCGGC
TACGGGGGTGAGGCCTGTGGCCAGTGTGGCCTTGGCTACTTTGAGGCAGAACGCAACGCC
AGCCATCTGGTATGTTCGGCTTGTTTTGGCCCCTGTGCCCGATGCTCAGGACCTGAGGAA
TCAAACTGTTTGCAATGCAAGAAGGGCTGGGCCCTGCATCACCTCAAGTGTGTAGACATT
GATGAGTGTGGCACAGAGGGAGCCAACTGTGGAGCTGACCAATTCTGCGTGAACACTGAG
GGCTCCTATGAGTGCCGAGACTGTGCCAAGGCCTGCCTAGGCTGCATGGGGGCAGGGCCA
GGTCGCTGTAAGAAGTGTAGCCCTGGCTATCAGCAGGTGGGCTCCAAGTGTCTCGATGTG
GATGAGTGTGAGACAGAGGTGTGTCCGGGAGAGAACAAGCAGTGTGAAAACACCGAGGGC
GGTTATCGCTGCATCTGTGCCGAGGGCTACAAGCAGATGGAAGGCATCTGTGTGAAGGAG
CAGATCCCAGAGTCAGCAGGCTTCTTCTCAGAGATGACAGAAGACGAGTTGGTGGTGCTG
CAGCAGATGTTCTTTGGCATCATCATCTGTGCACTGGCCACGCTGGCTGCTAAGGGCGAC
TTGGTGTTCACCGCCATCTTCATTGGGGCTGTGGCGGCCATGACTGGCTACTGGTTGTCA
GAGCGCAGTGACCGTGTGCTGGAGGGCTTCATCAAGGGCAGATAATCGCGGCCACCACCT
GTAGGACCTCCTCCCACCCACGCTGCCCCCAGAGCTTGGGCTGCCCTCCTGCTGGACACT
CAGGACAGCTTGGTTTATTTTTGAGAGTGGGGTAAGCACCCCTACCTGCCTTACAGAGCA
GCCCAGGTACCCAGGCCCGGGCAGACAAGGCCCCTGGGGTAAAAAGTAGCCCTGAAGGTG
GATACCATGAGCTCTTCACCTGGCGGGGACTGGCAGGCTTCACAATGTGTGAATTTCAAA
AGTTTTTCCTTAATGGTGGCTGCTAGAGCTTTGGCCCCTGCTTAGGATTAGGTGGTCCTC
ACAGGGGTGGGGCCATCACAGCTCCCTCCTGCCAGCTGCATGCTGCCAGTTCCTGTTCTG
TGTTCACCACATCCCCACACCCCATTGCCACTTATTTATTCATCTCAGGAAATAAAGAAA
GGTCTTGGAAAGTTAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 18

MAPWPPKGLVPAVLWGLSLFLNLPGPIWLQPSPPPQSSPPPQPHPCHTCRGLVDSFNKGL
ERTIRDNFGGGNTAWEEENLSKYKDSETRLVEVLEGVCSKSDFECHRLLELSEELVESWW
FHKQQEAPDLFQWLCSDSLKLCCPAGTFGPSCLPCPGGTERPCGGYGQCEGEGTRGGSGH
CDCQAGYGGEACGQCGLGYFEAERNASHLVCSACFGPCARCSGPEESNCLQCKKGWALHH
LKCVDIDECGTEGANCGADQFCVNTEGSYECRDCAKACLGCMGAGPGRCKKCSPGYQQVG
SKCLDVDECETEVCPGENKQCENTEGGYRCICAEGYKQMEGICVKEQIPESAGFFSEMTE
DELVVLQQMFFGIIICALATLAAKGDLVFTAIFIGAVAAMTGYWLSERSDRVLEGFIKGR

FIGURE 19

GCCCGGGACTGGCGCAAGGTGCCCAAGCAAGGAAAGAAATAATGAAGAGACACATGTGTT
AGCTGCAGCCTTTTGAAACACGCAAGAAGGAAATCAATAGTGTGGACAGGGCTGGAACCT
TTACCACGCTTGTTGGAGTAGATGAGGAATGGGCTCGTGATTATGCTGACATTCCAGCAT
GAATCTGGTAGACCTGTGGTTAACCCGTTCCCTCTCCATGTGTCTCCTCCTACAAAGTTT
TGTTCTTATGATACTGTGCTTTCATTCTGCCAGTATGTGTCCCAAGGGCTGTCTTTGTTC
TTCCTCTGGGGGTTTAAATGTCACCTGTAGCAATGCAAATCTCAAGGAAATACCTAGAGA
TCTTCCTCCTGAAACAGTCTTACTGTATCTGGACTCCAATCAGATCACATCTATTCCCAA
TGAAATTTTTAAGGACCTCCATCAACTGAGAGTTCTCAACCTGTCCAAAAATGGCATTGA
GTTTATCGATGAGCATGCCTTCAAAGGAGTAGCTGAAACCTTGCAGACTCTGGACTTGTC
CGACAATCGGATTCAAAGTGTGCACAAAAATGCCTTCAATAACCTGAAGGCCAGGGCCAG
AATTGCCAACAACCCCTGGCACTGCGACTGTACTCTACAGCAAGTTCTGAGGAGCATGGC
GTCCAATCATGAGACAGCCCACAACGTGATCTGTAAAACGTCCGTGTTGGATGAACATGC
TGGCAGACCATTCCTCAATGCTGCCAACGACGCTGACCTTTGTAACCTCCCTAAAAAAAC
TACCGATTATGCCATGCTGGTCACCATGTTTGGCTGGTTCACTATGGTGATCTCATATGT
GGTATATTATGTGAGGCAAAATCAGGAGGATGCCCGGAGACACCTCGAATACTTGAAATC
CCTGCCAAGCAGGCAGAAGAAAGCAGATGAACCTGATGATATTAGCACTGTGGTATAGTG
TCCAAACTGACTGTCATTGAGAAAGAAAGAAAGTAGTTTGCGATTGCAGTAGAAATAAGT
GGTTTACTTCTCCCATCCATTGTAAACATTTGAAACTTTGTATTTCAGTTTTTTTTGAAT
TATGCCACTGCTGAACTTTTAACAAACACTACAACATAAATAATTTGAGTTTAGGTGATC
CACCCCTTAATTGTACCCCCGATGGTATATTTCTGAGTAAGCTACTATCTGAACATTAGT
TAGATCCATCTCACTATTTAATAATGAAATTTATTTTTTTAATTTAAAGCAAATAAAAG
CTTAACTTTGAACCATGGAAAAAAAAAAAAAAAAAAAAAAAAAACA

FIGURE 20

MNLVDLWLTRSLSMCLLLQSFVLMILCFHSASMCPKGCLCSSSGGLNVTCSNANLKEIPR
DLPPETVLLYLDSNQITSIPNEIFKDLHQLRVLNLSKNGIEFIDEHAFKGVAETLQTLDL
SDNRIQSVHKNAFNNLKARARIANNPWHCDCTLQQVLRSMASNHETAHNVICKTSVLDEH
AGRPFLNAANDADLCNLPKKTTDYAMLVTMFGWFTMVISYVVYYVRQNQEDARRHLEYLK
SLPSRQKKADEPDDISTVV

Signal sequence:
amino acids 1-33

Transmembrane domain:
amino acids 205-220

N-glycosylation site:
amino acids 47-51, 94-98

cAMP- and cGMP-dependent protein kinase phosphorylation site:
amino acids 199-203

Casein kinase II phosphorylation site:
amino acids 162-166, 175-179

N-myristoylation site:
amino acids 37-43, 45-51, 110-116

FIGURE 21

CGCCACCACTGCGGCCACCGCCAATGAAACGCCTCCCGCTCCTAGTGGTTTTTCCACTT
TGTTGAATTGTTCCTATACTCAAAATTGCACCAAGACACCTTGTCTCCCAAATGCAAAAT
GTGAAATACGCAATGGAATTGAAGCCTGCTATTGCAACATGGGATTTTCAGGAAATGGTG
TCACAATTTGTGAAGATGATAATGAATGTGGAAATTTAACTCAGTCCTGTGGCGAAAATG
CTAATTGCACTAACACAGAAGGAAGTTATTATTGTATGTGTGTACCTGGCTTCAGATCCA
GCAGTAACCAAGACAGGTTTATCACTAATGATGGAACCGTCTGTATAGAAAATGTGAATG
CAAACTGCCATTTAGATAATGTCTGTATAGCTGCAAATATTAATAAAACTTTAACAAAAA
TCAGATCCATAAAAGAACCTGTGGCTTTGCTACAAGAAGTCTATAGAAATTCTGTGACAG
ATCTTTCACCAACAGATATAATTACATATATAGAAATATTAGCTGAATCATCTTCATTAC
TAGGTTACAAGAACAACACTATCTCAGCCAAGGACACCCTTTCTAACTCAACTCTTACTG
AATTTGTAAAAACCGTGAATAATTTTGTTCAAAGGGATACATTTGTAGTTTGGGACAAGT
TATCTGTGAATCATAGGAGAACACATCTTACAAAACTCATGCACACTGTTGAACAAGCTA
CTTTAAGGATATCCCAGAGCTTCCAAAAGACCACAGAGTTTGATACAAATTCAACGGATA
TAGCTCTCAAAGTTTTCTTTTTTGATTCATATAACATGAAACATATTCATCCTCATATGA
ATATGGATGGAGACTACATAAATATATTTCCAAAGAGAAAAGCTGCATATGATTCAAATG
GCAATGTTGCAGTTGCATTTTTATATTATAAGAGTATTGGTCCTTTGCTTTCATCATCTG
ACAACTTCTTATTGAAACCTCAAAATTATGATAATTCTGAAGAGGAGGAAAGAGTCATAT
CTTCAGTAATTTCAGTCTCAATGAGCTCAAACCCACCCACATTATATGAACTTGAAAAAA
TAACATTTACATTAAGTCATCGAAAGGTCACAGATAGGTATAGGAGTCTATGTGCATTTT
GGAATTACTCACCTGATACCATGAATGGCAGCTGGTCTTCAGAGGGCTGTGAGCTGACAT
ACTCAAATGAGACCCACACCTCATGCCGCTGTAATCACCTGACACATTTTGCAATTTTGA
TGTCCTCTGGTCCTTCCATTGGTATTAAAGATTATAATATTCTTACAAGGATCACTCAAC
TAGGAATAATTATTTCACTGATTTGTCTTGCCATATGCATTTTTACCTTCTGGTTCTTCA
GTGAAATTCAAAGCACCAGGACAACAATTCACAAAAATCTTTGCTGTAGCCTATTTCTTG
CTGAACTTGTTTTTCTTGTTGGGATCAATACAAATACTAATAAGCTCTTCTGTTCAATCA
TTGCCGGACTGCTACACTACTTCTTTTTAGCTGCTTTTGCATGGATGTGCATTGAAGGCA
TACATCTCTATCTCATTGTTGTGGGTGTCATCTACAACAAGGGATTTTTGCACAAGAATT
TTTATATCTTTGGCTATCTAAGCCCAGCCGTGGTAGTTGGATTTTCGGCAGCACTAGGAT
ACAGATATTATGGCACAACCAAAGTATGTTGGCTTAGCACCGAAAACAACTTTATTTGGA
GTTTTATAGGACCAGCATGCCTAATCATTCTTGTTAATCTCTTGGCTTTTGGAGTCATCA
TATACAAAGTTTTTCGTCACACTGCAGGGTTGAAACCAGAAGTTAGTTGCTTTGAGAACA
TAAGGTCTTGTGCAAGAGGAGCCCTCGCTCTTCTGTTCCTTCTCGGCACCACCTGGATCT
TTGGGGTTCTCCATGTTGTGCACGCATCAGTGGTTACAGCTTACCTCTTCACAGTCAGCA
ATGCTTTCCAGGGGATGTTCATTTTTTTATTCCTGTGTGTTTTATCTAGAAAGATTCAAG
AAGAATATTACAGATTGTTCAAAAATGTCCCCTGTTGTTTTGGATGTTTAAGGTAAACAT
AGAGAATGGTGGATAATTACAACTGCACAAAAAATAAAAATTCCAAGCTGTGGATGACCAA
TGTATAAAAATGACTCATCAAATTATCCAATTATTAACTACTAGACAAAAAGTATTTTAA
ATCAGTTTTTCTGTTTATGCTATAGGAACTGTAGATAATAAGGTAAAATTATGTATCATA
TAGATATACTATGTTTTTCTATGTGAAATAGTTCTGTCAAAAATAGTATTGCAGATATTT
GGAAAGTAATTGGTTTCTCAGGAGTGATATCACTGCACCCAAGGAAAGATTTTCTTTCTA
ACACGAGAAGTATATGAATGTCCTGAAGGAAACCACTGGCTTGATATTTCTGTGACTCGT
GTTGCCTTTGAAACTAGTCCCCTACCACCTCGGTAATGAGCTCCATTACAGAAAGTGGAA
CATAAGAGAATGAAGGGGCAGAATATCAAACAGTGAAAAGGGAATGATAAGATGTATTTT
GAATGAACTGTTTTTTCTGTAGACTAGCTGAGAAATTGTTGACATAAAATAAAGAATTGA
AGAAACACATTTTACCATTTTGTGAATTGTTCTGAACTTAAATGTCCACTAAAACAACTT
AGACTTCTGTTTGCTAAATCTGTTTCTTTTTCTAATATTCTAAAAAAAAAAAAAAGGTTT
ACCTCCACAAATTGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 22

MKRLPLLVVFSTLLNCSYTQNCTKTPCLPNAKCEIRNGIEACYCNMGFSGNGVTICEDDN
ECGNLTQSCGENANCTNTEGSYYCMCVPGFRSSSNQDRFITNDGTVCIENVNANCHLDNV
CIAANINKTLTKIRSIKEPVALLQEVYRNSVTDLSPTDIITYIEILAESSSLLGYKNNTI
SAKDTLSNSTLTEFVKTVNNFVQRDTFVVWDKLSVNHRRTHLTKLMHTVEQATLRISQSF
QKTTEFDTNSTDIALKVFFFDSYNMKHIHPHMNMDGDYINIFPKRKAAYDSNGNVAVAFL
YYKSIGPLLSSSDNFLLKPQNYDNSEEEERVISSVISVSMSSNPPTLYELEKITFTLSHR
KVTDRYRSLCAFWNYSPDTMNGSWSSEGCELTYSNETHTSCRCNHLTHFAILMSSGPSIG
IKDYNILTRITQLGIIISLICLAICIFTFWFFSEIQSTRTTIHKNLCCSLFLAELVFLVG
INTNTNKLFCSIIAGLLHYFFLAAFAWMCIEGIHLYLIVVGVIYNKGFLHKNFYIFGYLS
PAVVVGFSAALGYRYYGTTKVCWLSTENNFIWSFIGPACLIIILVNLLAFGVIIYKVFRHT
AGLKPEVSCFENIRSCARGALALLFLLGTTWIFGVLHVVHASVVTAYLFTVSNAFQGMFI
FLFLCVLSRKIQEEYYRLFKNVPCCFGCLR

FIGURE 23

CTCCTCTTAACATACTTGCAGCTAAAACTAAATATTGCTGCTTGGGGACCTCCTTCTAGC
CTTAAATTTCAGCTCATCACCTTCACCTGCCTTGGTCATGGCTCTGCTATTCTCCTTGAT
CCTTGCCATTTGCACCAGACCTGGATTCCTAGCGTCTCCATCTGGAGTGCGGCTGGTGGG
GGGCCTCCACCGCTGTGAAGGGCGGGTGGAGGTGGAACAGAAAGGCCAGTGGGGCACCGT
GTGTGATGACGGCTGGGACATTAAGGACGTGGCTGTGTTGTGCCGGGAGCTGGGCTGTGG
AGCTGCCAGCGGAACCCCTAGTGGTATTTTGTATGAGCCACCAGCAGAAAAAGAGCAAAA
GGTCCTCATCCAATCAGTCAGTTGCACAGGAACAGAAGATACATTGGCTCAGTGTGAGCA
AGAAGAAGTTTATGATTGTTCACATGATGAAGATGCTGGGGCATCGTGTGAGAACCCAGA
GAGCTCTTTCTCCCCAGTCCCAGAGGGTGTCAGGCTGGCTGACGGCCCTGGGCATTGCAA
GGGACGCGTGGAAGTGAAGCACCAGAACCAGTGGTATACCGTGTGCCAGACAGGCTGGAG
CCTCCGGGCCGCAAAGGTGGTGTGCCGGCAGCTGGGATGTGGGAGGGCTGTACTGACTCA
AAAACGCTGCAACAAGCATGCCTATGGCCGAAAACCCATCTGGCTGAGCCAGATGTCATG
CTCAGGACGAGAAGCAACCCTTCAGGATTGCCCTTCTGGGCCTTGGGGGAAGAACACCTG
CAACCATGATGAAGACACGTGGGTCGAATGTGAAGATCCCTTTGACTTGAGACTAGTAGG
AGGAGACAACCTCTGCTCTGGGCGACTGGAGGTGCTGCACAAGGGCGTATGGGGCTCTGT
CTGTGATGACAACTGGGGAGAAAAGGAGGACCAGGTGGTATGCAAGCAACTGGGCTGTGG
GAAGTCCCTCTCTCCCTCCTTCAGAGACCGGAAATGCTATGGCCCTGGGGTTGGCCGCAT
CTGGCTGGATAATGTTCGTTGCTCAGGGGAGGAGCAGTCCCTGGAGCAGTGCCAGCACAG
ATTTTGGGGGTTTCACGACTGCACCCACCAGGAAGATGTGGCTGTCATCTGCTCAGTGTA
GGTGGGCATCATCTAATCTGTTGAGTGCCTGAATAGAAGAAAAACACAGAAGAAGGGAGC
ATTTACTGTCTACATGACTGCATGGGATGAACACTGATCTTCTTCTGCCCTTGGACTGGG
ACTTATACTTGGTGCCCCTGATTCTCAGGCCTTCAGAGTTGGATCAGAACTTACAACATC
AGGTCTAGTTCTCAGGCCATCAGACATAGTTTGGAACTACATCACCACCTTTCCTATGTC
TCCACATTGCACACAGCAGATTCCCAGCCTCCATAATTGTGTGTATCAACTACTTAAATA
CATTCTCACACACACACACACACACACACACACACACACACACACATACACCATTTGTCC
TGTTTCTCTGAAGAACTCTGACAAAATACAGATTTTGGTACTGAAAGAGATTCTAGAGGA
ACGGAATTTTAAGGATAAATTTTCTGAATTGGTTATGGGGTTTCTGAAATTGGCTCTATA
ATCTAATTAGATATAAAATTCTGGTAACTTTATTTACAATAATAAAGATAGCACTATGTG
TTCAAA

FIGURE 24

MALLFSLILAICTRPGFLASPSGVRLVGGLHRCEGRVEVEQKGQWGTVCDDGWDIKDVAV
LCRELGCGAASGTPSGILYEPPAEKEQKVLIQSVSCTGTEDTLAQCEQEEVYDCSHDEDA
GASCENPESSFSPVPEGVRLADGPGHCKGRVEVKHQNQWYTVCQTGWSLRAAKVVCRQLG
CGRAVLTQKRCNKHAYGRKPIWLSQMSCSGREATLQDCPSGPWGKNTCNHDEDTWVECED
PFDLRLVGGDNLCSGRLEVLHKGVWGSVCDDNWGEKEDQVVCKQLGCGKSLSPSFRDRKC
YGPGVGRIWLDNVRCSGEEQSLEQCQHRFWGFHDCTHQEDVAVICSV

Signal sequence:
amino acids 1-15

Casein kinase II phosphorylation site:
amino acids 47-51, 97-101, 115-119, 209-213, 214-218, 234-238, 267-271, 294-298, 316-320, 336-340

N-myristoylation site:
amino acids 29-35, 43-49, 66-72, 68-74, 72-78, 98-104, 137-143, 180-186, 263-269, 286-292

Amidation site:
amino acids 196-200

Speract receptor repeated domain signature:
amino acids 29-67, 249-287

FIGURE 25

CGGACGCGTGGGCGTCCGGCGGTCGCAGAGCCAGGAGGCGGAGGCGCGCGGGCCAGCCTG
GGCCCCAGCCCACACCTTCACCAGGGCCCAGGAGCCACC**ATG**TGGCGATGTCCACTGGGG
CTACTGCTGTTGCTGCCGCTGGCTGGCCACTTGGCTCTGGGTGCCCAGCAGGGTCGTGGG
CGCCGGGAGCTAGCACCGGGTCTGCACCTGCGGGGCATCCGGGACGCGGGAGGCCGGTAC
TGCCAGGAGCAGGACCTGTGCTGCCGCGGCCGTGCCGACGACTGTGCCCTGCCCTACCTG
GGCGCCATCTGTTACTGTGACCTCTTCTGCAACCGCACGGTCTCCGACTGCTGCCCTGAC
TTCTGGGACTTCTGCCTCGGCGTGCCACCCCCTTTTCCCCCGATCCAAGGATGTATGCAT
GGAGGTCGTATCTATCCAGTCTTGGGAACGTACTGGGACAACTGTAACCGTTGCACCTGC
CAGGAGAACAGGCAGTGGCATGGTGGATCCAGACATGATCAAAGCCATCAACCAGGGCAA
CTATGGCTGGCAGGCTGGGAACCACAGCGCCTTCTGGGGCATGACCCTGGA**TGA**GGGCAT
TCGCTACCGCCTGGGCACCATCCGCCCATCTTCCTCGGTCATGAACATGCATGAAATTTA
TACAGTGCTGAACCCAGGGGAGGTGCTTCCCACAGCCTTCGAGGCCTCTGAGAAGTGGCC
CAACCTGATTCATGAGCCTCTTGACCAAGGCAACTGTGCAGGCTCCTGGGCCTTCTCCAC
AGCAGCTGTGGCATCCGATCGTGTCTCAATCCATTCTCTGGGACACATGACGCCTGTCCT
GTCGCCCCAGAACCTGCTGTCTTGTGACACCCACCAGCAGCAGGGCTGCCGCGGTGGGCG
TCTCGATGGTGCCTGGTGGTTCCTGCGTCGCCGAGGGGTGGTGTCTGACCACTGCTACCC
CTTCTCGGGCCGTGAACGAGACGAGGCTGGCCCTGCGCCCCCCTGTATGATGCACAGCCG
AGCCATGGGTCGGGGCAAGCGCCAGGCCACTGCCCACTGCCCCAACAGCTATGTTAATAA
CAATGACATCTACCAGGTCACTCCTGTCTACCGCCTCGGCTCCAACGACAAGGAGATCAT
GAAGGAGCTGATGGAGAATGGCCCTGTCCAAGCCCTCATGGAGGTGCATGAGGACTTCTT
CCTATACAAGGGAGGCATCTACAGCCACACGCCAGTGAGCCTTGGGAGGCCAGAGAGATA
CCGCCGGCATGGGACCCACTCAGTCAAGATCACAGGATGGGGAGAGGAGACGCTGCCAGA
TGGAAGGACGCTCAAATACTGGACTGCGGCCAACTCCTGGGGCCCAGCCTGGGGCGAGAG
GGGCCACTTCCGCATCGTGCGCGGCGTCAATGAGTGCGACATCGAGAGCTTCGTGCTGGG
CGTCTGGGGCCGCGTGGGCATGGAGGACATGGGTCATCACTGAGGCTGCGGGCACCACGC
GGGGTCCGGCCTGGGATCCAGGCTAAGGGCCGGCGGAAGAGGCCCCAATGGGGCGGTGAC
CCCAGCCTCGCCCGACAGAGCCCGGGGCGCAGGCGGGCGCCAGGGCGCTAATCCCGGCGC
GGGTTCCGCTGACGCAGCGCCCCGCCTGGGAGCCGCGGGCAGGCGAGACTGGCGGAGCCC
CCAGACCTCCCAGTGGGGACGGGGCAGGGCCTGGCCTGGGAAGAGCACAGCTGCAGATCC
CAGGCCTCTGGCGCCCCCACTCAAGACTACCAAAGCCAGGACACCTCAAGTCTCCAGCCC
CAATACCCCACCCCAATCCCGTATTCTTTTTTTTTTTTTTTTAGACAGGGTCTTGCTCCG
TTGCCCAGGTTGGAGTGCAGTGGCCCATCAGGGCTCACTGTAACCTCCGACTCCTGGGTT
CAAGTGACCCTCCCACCTCAGCCTCTCAAGTAGCTGGGACTACAGGTGCACCACCACACC
TGGCTAATTTTTGTATTTTTTGTAAAGAGGGGGTCTCACTGTGTTGCCCAGGCTGGTTT
CGAACTCCTGGGCTCAAGCGGTCCACCTGCCTCCGCCTCCCAAAGTGCTGGGATTGCAGG
CATGAGCCACTGCACCCAGCCCTGTATTCTTATTCTTCAGATATTTATTTTTCTTTTCAC
TGTTTTAAAATAAAACCAAAGTATTGATAAAAAAAAA

FIGURE 26

MWRCPLGLLLLLPLAGHLALGAQQGRGRRELAPGLHLRGIRDAGGRYCQEQDLCCRGRAD
DCALPYLGAICYCDLFCNRTVSDCCPDFWDFCLGVPPPFPPIQGCMHGGRIYPVLGTYWD
NCNRCTCQENRQWHGGSRHDQSHQPGQLWLAGWEPQRLLGHDPG

N-glycosylation site:
amino acids 78-82, 161-165

Casein kinase II phosphorylation site:
amino acids 80-84, 117-121, 126-130, 169-173, 205-209, 296-300, 411-415

N-myristoylation site:
amino acids 21-27, 39-45, 44-50, 104-110, 160-164, 224-230, 269-275, 378-384, 442-448

Amidation site:
amino acids 26-30, 318-322

Eukaryotic thiol (cysteine) proteases histidine active site:
amino acids 398-409

FIGURE 27

CCCACGCGTCCGGCAGGTTTTTCTTCAAGCCAAGAAGGACACGGATTGGCTGAAGGAGAA
AGTGCAGAGCTTGCAGACACTGGCTGCCAACAACTCTGCGTTGGCCAAAGCCAACAACGA
CACCCTGGAGGATATGAACAGCCAGCTCAACTCATTCACAGGTCAGATGGAGAACATCAC
CACTATCTCTCAAGCCAACGAGCAGAACCTGAAAGACCTGCAGGACTTACACAAAGATGC
AGAGAATAGAACAGCCATCAAGTTCAACCAACTGGAGGAACGCTTCCAGCTCTTTGAGAC
GGATATTGTGAACATCATTAGCAATATCAGTTACACAGCCCACCACCTGCGGACGCTGAC
CAGCAATCTAAATGA**AGT**CAGGACCACTTGCACAGATACCTTACCAAACACACAGATGAT
CTGACCTCCTTGAATAATACCCTGGCCAACATCCGTTTGGATTCTGTTTCTCTCAGGATG
CAACAAGATTTGATGAGGTCGAGGTTAGACACTGAAGTAGCCAACTTATCAGTGATTATG
GAAGAAATGAAGCTAGTAGACTCCAAGCATGGTCAGCTCATCAAGAATTTTACAATACTA
CAAGGTCCACCGGGCCCCAGGGGTCCAAGAGGTGACAGAGGATCCCAGGGACCCCCTGGC
CCAACTGGCAACAAGGGACAGAAAGGAGAGAAGGGGGAGCCTGGACCACCTGGCCCTGCG
GGTGAGAGAGGCCCAATTGGACCAGCTGGTCCCCCCGGAGAGCGTGGCGGCAAAGGATCT
AAAGGCTCCCAGGGCCCCAAAGGCTCCCGTGGTTCCCCTGGGAAGCCCGGCCCTCAGGGC
CCCAGTGGGGACCCAGGCCCCCCGGGCCCACCAGGCAAAGAGGGACTCCCCGGCCCTCAG
GGCCCTCCTGGCTTCCAGGGACTTCAGGGCACCGTTGGGGAGCCTGGGGTGCCTGGACCT
CGGGGACTGCCAGGCTTGCCTGGGGTACCAGGCATGCCAGGCCCCAAGGGCCCCCCCGGC
CCTCCTGGCCCATCAGGAGCGGTGGTGCCCCTGGCCCTGCAGAATGAGCCAACCCCGGCA
CCGGAGGACAATAGCTGCCCGCCTCACTGGAAGAACTTCACAGACAAATGCTACTATTTT
TCAGTTGAGAAAGAAATTTTTGAGGATGCAAAGCTTTTCTGTGAAGACAAGTCTTCACAT
CTTGTTTTCATAAACACTAGAGAGGAACAGCAATGGATAAAAAAACAGATGGTAGGGAGA
GAGAGCCACTGGATCGGCCTCACAGACTCAGAGCGTGAAAATGAATGGAAGTGGCTGGAT
GGGACATCTCCAGACTACAAAAATTGGAAAGCTGGACAGCCGGATAACTGGGGTCATGGC
CATGGGCCAGGAGAAGACTGTGCTGGGTTGATTTATGCTGGGCAGTGGAACGATTTCCAA
TGTGAAGACGTCAATAACTTCATTTGCGAAAAAGACAGGGAGACAGTACTGTCATCTGCA
TTA**TAA**CGGACTGTGATGGGATCACATGAGCAAATTTTCAGCTCTCAAAGGCAAAGGACA
CTCCTTTCTAATTGCATCACCTTCTCATCAGATTGAAAAAAAAAAAGCACTGAAAACCAA
TTACTGAAAAAAAATTGACAGCTAGTGTTTTTTACCATCCGTCATTACCCAAAGACTTGG
GAACTAAAATGTTCCCCAGGGTGATATGCTGATTTTCATTGTGCACATGGACTGAATCAC
ATAGATTCTCCTCCGTCAGTAACCGTGCGATTATACAAATTATGTCTTCCAAAGTATGGA
ACACTCCAATCAGAAAAAGGTTATCATTGGTCGTTGAGTTATGGGAAGAACTTAAGCATA
TACTGTGTAAACAGTGCCATACATTTCTAAAATCCCAAGTGTAGGAAAAATATGCAGACA
TACAGATATATAGGCCAACTATTAGTAATAATATGAAATATACTTAAAGAGCTTTTAAAA
CTTTGTATTTTTGTACAAAAAAAAA

FIGURE 28

MQQDLMRSRLDTEVANLSVIMEEMKLVDSKHGQLIKNFTILQGPPGPRGPRGDRGSQGPP
GPTGNKGQKGEKGEPGPPGPAGERGPIGPAGPPGERGGKGSKGSQGPKGSRGSPGKPGPQ
GPSGDPGPPGPPGKEGLPGPQGPPGFQGLQGTVGEPGVPGPRGLPGLPGVPGMPGPKGPP
GPPGPSGAVVPLALQNEPTPAPEDNSCPPHWKNFTDKCYYFSVEKEIFEDAKLFCEDKSS
HLVFINTREEQQWIKKQMVGRESHWIGLTDSERENEWKWLDGTSPDYKNWKAGQPDNWGH
GHGPGEDCAGLIYAGQWNDFQCEDVNNFICEKDRETVLSSAL

Signal sequence:
None

Transmembrane domain:
None

N-glycosylation site:
16-19, 37-40, 213-216

Tyrosine kinase phosphorylation site:
212-220

N-myristoylation site:
97-102, 100-105, 148-153, 267-272, 293-298, 310-315

Cell attachment sequence:
51-53

C-type lectin domain signature:
308-330

Lectin C-type domain:
233-330

Collagen triple helix repeat:
43-102, 127-186

FIGURE 29

GGACTAATCTGTGGGAGCAGTTTATTCCAGTATCACCCAGGGTGCAGCCACACCAGGACT
GTGTTGAAGGGTGTTTTTTTTCTTTTAAATGTAATACCTCCTCATCTTTTCTTCTTACAC
AGTGTCTGAGAACATTTACATTATAGATAAGTAGTACATGGTGGATAACTTCTACTTTTA
GGAGGACTACTCTCTTCTGACAGTCCTAGACTGGTCTTCTACACTAAGACACC**ATG**AAGG
AGTATGTGCTCCTATTATTCCTGGCTTTGTGCTCTGCCAAACCCTTCTTTAGCCCTTCAC
ACATCGCACTGAAGAATATGATGCTGAAGGATATGGAAGACACAGATGATGATGATGATG
ATGATGATGATGATGATGATGATGAGGACAACTCTCTTTTTCCAACAAGAGAGCCAAGAA
GCCATTTTTTTCCATTTGATCTGTTTCCAATGTGTCCATTTGGATGTCAGTGCTATTCAC
GAGTTGTACATTGCTCAGATTTAGGTTTGACCTCAGTCCCAACCAACATTCCATTTGATA
CTCGAATGCTTGATCTTCAAAACAATAAAATTAAGGAAATCAAAGAAAATGATTTTAAAG
GACTCACTTCACTTTATGGTCTGATCCTGAACAACAACAAGCTAACGAAGATTCACCCAA
AAGCCTTTCTAACCACAAAGAAGTTGCGAAGGCTGTATCTGTCCCACAATCAACTAAGTG
AAATACCACTTAATCTTCCCAAATCATTAGCAGAACTCAGAATTCATGAAAATAAAGTTA
AGAAAATACAAAAGGACACATTCAAAGGAATGAATGCTTTACACGTTTTGGAAATGAGTG
CAAACCCTCTTGATAATAATGGGATAGAGCCAGGGGCATTTGAAGGGGTGACGGTGTTCC
ATATCAGAATTGCAGAAGCAAAACTGACCTCAGTTCCTAAAGGCTTACCACCAACTTTAT
TGGAGCTTCACTTAGATTATAATAAAATTTCAACAGTGGAACTTGAGGATTTTAAACGAT
ACAAAGAACTACAAAGGCTGGGCCTAGGAAACAACAAAATCACAGATATCGAAAATGGGA
GTCTTGCTAACATACCACGTGTGAGAGAAATACATTTGGAAAACAATAAACTAAAAAAAA
TCCCTTCAGGATTACCAGAGTTGAAATACCTCCAGATAATCTTCCTTCATTCTAATTCAA
TTGCAAGAGTGGGAGTAAATGACTTCTGTCCAACAGTGCCAAAGATGAAGAAATCTTTAT
ACAGTGCAATAAGTTTATTCAACAACCCGGTGAAATACTGGGAAATGCAACCTGCAACAT
TTCGTTGTGTTTTGAGCAGAATGAGTGTTCAGCTTGGGAACTTTGGAATG**TAA**TAATTAG
TAATTGGTAATGTCCATTTAATATAAGATTCAAAAATCCCTACATTTGGAATACTTGAAC
TCTATTAATAATGGTAGTATTATATATACAAGCAAATATCTATTCTCAAGTGGTAAGTCC
ACTGACTTATTTTATGACAAGAAATTTCAACGGAATTTTGCCAAACTATTGATACATAAG
GGGTTGAGAGAAACAAGCATCTATTGCAGTTTCCTTTTTGCGTACAAATGATCTTACATA
AATCTCATGCTTGACCATTCCTTTCTTCATAACAAAAAAGTAAGATATTCGGTATTTAAC
ACTTTGTTATCAAGCACATTTTAAAAAGAACTGTACTGTAAATGGAATGCTTGACTTAGC
AAAATTTGTGCTCTTTCATTTGCTGTTAGAAAAACAGAATTAACAAAGACAGTAATGTGA
AGAGTGCATTACACTATTCTTATTCTTTAGTAACTTGGGTAGTACTGTAATATTTTTAAT
CATCTTAAAGTATGATTTGATATAATCTTATTGAAATTACCTTATCATGTCTTAGAGCCC
GTCTTTATGTTTAAAACTAATTTCTTAAAATAAAGCCTTCAGTAAATGTTCATTACCAAC
TTGATAAATGCTACTCATAAGAGCTGGTTTGGGGCTATAGCATATGCTTTTTTTTTTTTA
ATTATTACCTGATTTAAAAATCTCTGTAAAAACGTGTAGTGTTTCATAAAATCTGTAACT
CGCATTTTAATGATCCGCTATTATAAGCTTTTAATAGCATGAAAATTGTTAGGCTATATA
ACATTGCCACTTCAACTCTAAGGAATATTTTTGAGATATCCCTTTGGAAGACCTTGCTTG
GAAGAGCCTGGACACTAACAATTCTACACCAAATTGTCTCTTCAAATACGTATGGACTGG
ATAACTCTGAGAAACACATCTAGTATAACTGAATAAGCAGAGCATCAAATTAAACAGACA
GAAACCGAAAGCTCTATATAAATGCTCAGAGTTCTTTATGTATTTCTTATTGGCATTCAA
CATATGTAAAATCAGAAAACAGGGAAATTTTCATTAAAAATATTGGTTTGAAT

FIGURE 30

MKEYVLLLFLALCSAKPFFSPSHIALKNMMLKDMEDTDDDDDDDDDDDDDDEDNSLFPTRE
PRSHFFPFDLFPMCPFGCQCYSRVVHCSDLGLTSVPTNIPFDTRMLDLQNNKIKEIKEND
FKGLTSLYGLILNNNKLTKIHPKAFLTTKKLRRLYLSHNQLSEIPLNLPKSLAELRIHEN
KVKKIQKDTFKGMNALHVLEMSANPLDNNGIEPGAFEGVTVFHIRIAEAKLTSVPKGLPP
TLLELHLDYNKISTVELEDFKRYKELQRLGLGNNKITDIENGSLANIPRVREIHLENNKL
KKIPSGLPELKYLQIIFLHSNSIARVGVNDFCPTVPKMKKSLYSAISLFNNPVKYWEMQP
ATFRCVLSRMSVQLGNFGM

Signal sequence:
amino acids 1-15

N-glycosylation site:
amino acids 281-285

N-myristoylation sites:
amino acids 129-135, 210-216, 214-220, 237-243, 270-276, 282-288

Leucine zipper pattern:
amino acids 154-176

FIGURE 31

AGCAGGGAAATCCGGATGTCTCGGTTATGAAGTGGAGCAGTGAGTGTGAGCCTCAACATA
GTTCCAGAACTCTCCATCCGGACTAGTTATTGAGCATCTGCCTCTCATATCACCAGTGGC
CATCTGAGGTGTTTCCCTGGCTCTGAAGGGGTAGGCACGATGGCCAGGTGCTTCAGCCTG
GTGTTGCTTCTCACTTCCATCTGGACCACGAGGCTCCTGGTCCAAGGCTCTTTGCGTGCA
GAAGAGCTTTCCATCCAGGTGTCATGCAGAATTATGGGGATCACCCTTGTGAGCAAAAAG
GCGAACCAGCAGCTGAATTTCACAGAAGCTAAGGAGGCCTGTAGGCTGCTGGGACTAAGT
TTGGCCGGCAAGGACCAAGTTGAAACAGCCTTGAAAGCTAGCTTTGAAACTTGCAGCTAT
GGCTGGGTTGGAGATGGATTCGTGGTCATCTCTAGGATTAGCCCAAACCCCAAGTGTGGG
AAAAATGGGGTGGGTGTCCTGATTTGGAAGGTTCCAGTGAGCCGACAGTTTGCAGCCTAT
TGTTACAACTCATCTGATACTTGGACTAACTCGTGCATTCCAGAAATTATCACCACCAAA
GATCCCATATTCAACACTCAAACTGCAACACAAACAACAGAATTTATTGTCAGTGACAGT
ACCTACTCGGTGGCATCCCCTTACTCTACAATACCTGCCCCTACTACTACTCCTCCTGCT
CCAGCTTCCACTTCTATTCCACGGAGAAAAAAATTGATTTGTGTCACAGAAGTTTTTATG
GAAACTAGCACCATGTCTACAGAAACTGAACCATTTGTTGAAAATAAAGCAGCATTCAAG
AATGAAGCTGCTGGGTTTGGAGGTGTCCCCACGGCTCTGCTAGTGCTTGCTCTCCTCTTC
TTTGGTGCTGCAGCTGGTCTTGGATTTTGCTATGTCAAAAGGTATGTGAAGGCCTTCCCT
TTTACAAACAAGAATCAGCAGAAGGAAATGATCGAAACCAAAGTAGTAAAGGAGGAGAAG
GCCAATGATAGCAACCCTAATGAGGAATCAAAGAAAACTGATAAAAACCCAGAAGAGTCC
AAGAGTCCAAGCAAAACTACCGTGCGATGCCTGGAAGCTGAAGTTTAGATGAGACAGAAA
TGAGGAGACACACCTGAGGCTGGTTTCTTTCATGCTCCTTACCCTGCCCCAGCTGGGGAA
ATCAAAAGGGCCAAAGAACCAAAGAAGAAAGTCCACCCTTGGTTCCTAACTGGAATCAGC
TCAGGACTGCCATTGGACTATGGAGTGCACCAAAGAGAATGCCCTTCTCCTTATTGTAAC
CCTGTCTGGATCCTATCCTCCTACCTCCAAAGCTTCCCACGGCCTTTCTAGCCTGGCTAT
GTCCTAATAATATCCCACTGGGAGAAAGGAGTTTTGCAAAGTGCAAGGACCTAAAACATC
TCATCAGTATCCAGTGGTAAAAAGGCCTCCTGGCTGTCTGAGGCTAGGTGGGTTGAAAGC
CAAGGAGTCACTGAGACCAAGGCTTTCTCTACTGATTCCGCAGCTCAGACCCTTTCTTCA
GCTCTGAAAGAGAAACACGTATCCCACCTGACATGTCCTTCTGAGCCCGGTAAGAGCAAA
AGAATGGCAGAAAAGTTTAGCCCCTGAAAGCCATGGAGATTCTCATAACTTGAGACCTAA
TCTCTGTAAAGCTAAAATAAAGAAATAGAACAAGGCTGAGGATACGACAGTACACTGTCA
GCAGGGACTGTAAACACAGACAGGGTCAAAGTGTTTTCTCTGAACACATTGAGTTGGAAT
CACTGTTTAGAACACACACACTTACTTTTTCTGGTCTCTACCACTGCTGATATTTTCTCT
AGGAAATATACTTTTACAAGTAACAAAAATAAAAACTCTTATAAATTTCTATTTTTATCT
GAGTTACAGAAATGATTACTAAGGAAGATTACTCAGTAATTTGTTTAAAAAGTAATAAAA
TTCAACAAACATTTGCTGAATAGCTACTATATGTCAAGTGCTGTGCAAGGTATTACACTC
TGTAATTGAATATTATTCCTCAAAAAATTGCACATAGTAGAACGCTATCTGGGAAGCTAT
TTTTTTCAGTTTTGATATTTCTAGCTTATCTACTTCCAAACTAATTTTTATTTTTGCTGA
GACTAATCTTATTCATTTTCTCTAATATGGCAACCATTATAACCTTAATTTATTATTAAC
ATACCTAAGAAGTACATTGTTACCTCTATATACCAAAGCACATTTTAAAAGTGCCATTAA
CAAATGTATCACTAGCCCTCCTTTTTCCAACAAGAAGGGACTGAGAGATGCAGAAATATT
TGTGACAAAAAATTAAAGCATTTAGAAAACTT

FIGURE 32

MARCFSLVLLLTSIWTTRLLVQGSLRAEELSIQVSCRIMGITLVSKKANQQLNFTEAKEA
CRLLGLSLAGKDQVETALKASFETCSYGWVGDGFVVISRISPNPKCGKNGVGVLIWKVPV
SRQFAAYCYNSSDTWTNSCIPEIITTKDPIFNTQTATQTTEFIVSDSTYSVASPYSTIPA
PTTTPPAPASTSIPRRKKLICVTEVFMETSTMSTETEPFVENKAAFKNEAAGFGGVPTAL
LVLALLFFGAAAGLGFCYVKRYVKAFPFTNKNQQKEMIETKVVKEEKANDSNPNEESKKT
DKNPEESKSPSKTTVRCLEAEV

Signal sequence:
amino acids 1-16

Transmembrane domain:
amino acids 235-254

N-glycosylation site:
amino acids 53-57, 130-134, 289-293

Casein kinase II phosphorylation site:
amino acids 145-149, 214-218

Tyrosine kinase phosphorylation site:
amino acids 79-88

N-myristoylation site:
amino acids 23-29, 65-71, 234-240, 235-239, 249-255, 253-259

FIGURE 33

GAAAAAAAAAAAAAAAGGGAAGCAAGCTTAGCTGTACACCCTGAGTCTTGCAAAAGCTGCAG
CCCCACCCAGGAGCAGGGTGGTGGCTGGGGCGATGGTGGACGCCCTGAAGATGTCCC**ATG**
GCTACTGAAGGGGCTGCCCAGTTAGGGAACAGAGTGGCGGGCATGGTGTGTAGCCTATGG
GTGCTGCTCCTGGTGTCTTCAGTTCTGGCTCTGGAAGAGGTATTGCTGGACACCACCGGA
GAGACATCTGAGATTGGCTGGCTCACCTACCCACCAGGGGGGTGGGACGAGGTGAGTGTT
CTGGACGACCAGCGACGCCTGACTCGGACCTTTGAGGCATGTCATGTGGCAGGGGCCCCT
CCAGGCACCGGGCAGGACAATTGGTTGCAGACACACTTTGTGGAGCGGCGCGGGGCCCAG
AGGGCGCACATTCGACTCCACTTCTCTGTGCGGGCATGCTCCAGCCTGGGTGTGAGCGGC
GGCACCTGCCGGGAGACCTTCACCCTTTACTACCGTCAGGCTGAGGAGCCCGACAGCCCT
GACAGCGTTTCCTCCTGGCACCTCAAACGTTGGACCAAGGTGGACACAATTGCAGCAGAC
GAGAGCTTTCCATCCTCCTCCTCCTCCTCCTCCTCCTCTTCTTCCTCTGCAGCGTGGGCT
GTGGGACCCCACGGGGCTGGGCAGCGGGCTGGACTGCAACTGAACGTCAAAGAGCGGAGC
TTTGGGCCTCTCACCCAACGCGGCTTCTACGTGGCCTTCCAGGACACGGGGGCCTGCCTG
GCCCTGGTCGCTGTCAGGCTCTTCTCCTACACCTGCCCTGCCGTGCTCCGATCCTTTGCT
TCCTTTCCAGAGACGCAGGCCAGTGGGGCTGGGGGGGCCTCCCTGGTGGCAGCTGTGGGC
ACCTGTGTGGCTCATGCAGAGCCAGAGGAGGATGGAGTAGGGGGCCAGGCAGGAGGCAGC
CCCCCCAGGCTGCACTGCAACGGGGAGGGCAAGTGGATGGTAGCTGTCGGGGGCTGCCGC
TGCCAGCCTGGATACCAACCAGCACGAGGAGACAAGGCCTGCCAAGCCTGCCCACGGGGG
CTCTATAAGGCTTCTGCTGGGAATGCTCCCTGCTCACCATGCCCTGCCCGCAGTCACGCT
CCCAACCCAGCAGCCCCCGTTTGCCCCTGCCTGGAGGGCTTCTACCGGGCCAGTTCCGAC
CCACCAGAGGCCCCCTGCACTGGTCCTCCATCGGCTCCCCAGGAGCTTTGGTTTGAGGTG
CAAGGCTCAGCACTCATGCTACACTGGCGCCTGCCTCGGGAGCTGGGGGGTCGAGGGGAC
CTGCTCTTCAATGTCGTGTGCAAGGAGTGTGAAGGCCGCCAGGAACCTGCCAGCGGTGGT
GGGGGCACTTGTCACCGCTGCAGGGATGAGGTCCACTTCGACCCTCGCCAGAGAGGCCTG
ACTGAGAGCCGAGTGTTAGTGGGGGGACTCCGGGCACACGTACCCTACATCTTAGAGGTG
CAGGCTGTTAATGGGGTGTCTGAGCTCAGCCCTGACCCTCCTCAGGCTGCAGCCATCAAT
GTCAGCACCAGCCATGAAGTGCCCTCTGCTGTCCCTGTGGTGCACCAGGTGAGCCGGGCA
TCCAACAGCATCACGGTGTCCTGGCCGCAGCCCGACCAGACCAATGGGAACATCCTGGAC
TATCAGCTCCGCTACTATGACCAGGCAGAAGACGAATCCCACTCCTTCACCCTGACCAGC
GAGACCAACACTGCCACCGTGACACAGCTGAGCCCTGGCCACATCTATGGTTTCCAGGTG
CGGGCCCGGACTGCTGCCGGCCACGGCCCCTACGGGGGCAAAGTCTATTTCCAGACACTT
CCTCAAGGGGAGCTGTCTTCCCAGCTTCCGGAAAGACTCTCCTTGGTGATCGGCTCCACC
CTGGGGGCTTTGGCCTTCCTCCTGCTGGCAGCCATCACCGTGCTGGCGGTCGTCTTCCAG
CGGAAGCGGCGTGGGACTGGCTACACGGAGCAGCTGCAGCAATACAGCAGCCCAGGACTC
GGGGTGAAGTATTACATCGACCCCTCCACCTACGAGGACCCCTGTCAGGCCATCCGAGAA
CTTGCCCGGGAAGTCGATCCTGCTTATATCAAGATTGAGGAGGTCATTGGGACAGGCTCT
TTTGGAGAAGTGCGCCAGGGCCGCCTGCAGCCACGGGGACGGAGGGAGCAGACTGTGGCC
ATCCAGGCCCTGTGGGCCGGGGGCGCCGAAAGCCTGCAGATGACCTTCCTGGGCCGGGCC
GCAGTGCTGGGTCAGTTCCAGCACCCCAACATCCTGCGGCTGGAGGGCGTGGTCACCAAG
AGCCGACCCCTCATGGTGCTGACGGAGTTCATGGAGCTTGGCCCCCTGGACAGCTTCCTC
AGGCAGCGGGAGGGCCAGTTCAGCAGCCTGCAGCTGGTGGCCATGCAGCGGGGAGTGGCT
GCTGCCATGCAGTACCTGTCCAGCTTTGCCTTCGTCCATCGCTCGCTGTCTGCCCACAGC
GTGCTGGTGAATAGCCACTTGGTGTGCAAGGTGGCCCGTCTTGGCCACAGTCCTCAGGGC
CCAAGTTGTTTGCTTCGCTGGGCAGCCCCAGAGGTCATTGCACATGGAAAGCATACTCAT
GTGGGAAGTGATGAGTTATGGAGAACGGCCTTACTGGGACATGAG**TGA**GCAGGAGGTACT
AAATGCAATAGAGCAGGAGTTCCGGCTGCCCCCGCCTCCAGGCTGTCCTCCTGGATTACA

TCTACTTATGTTGGACACTTGGCAGAAGGACCGTGCCCGGCGGCCTCATTTTGACCAGCT
GGTGGCTGCATTTGACAAGATGATCCGCAAGCCAGATACCCTGCAGGCTGGCGGGGACCC
AGGGGAAAGGCCTTCCCAGGCCCTTCTGACCCCTGTGGCCCTGGACTTTCCTTGTCTGGA
CTCACCCCAGGCCTGGCTTTCAGCCATTGGACTGGAGTGCTACCAGGACAACTTCTCCAA
GTTTGGCCTCTGTACCTTCAGTGATGTGGCTCAGCTCAGCCTAGAAGACCTGCCTGCCCT
GGGCATCACCCTGGCTGGCCACCAGAAGAAGCTGCTGCACCACATCCAGCTCCTTCAGCA
ACACCTGAGGCAGCAGGGCTCAGTGGAGGTCTGAGAATGACGATACCCGTGACTCAGCCC
TGGACACTGGTCCGAGAAGGGACATGTGGGACGTGAGCCGGGCTCCAACAGCCTCTGTGA
GAGATGCCCCACACCAAACCCAACCCTCCGATGGCTGCATTCCCTGGTCCTCCGCTTTTC
CACCAGCCCCCTCCTCATTAAAGGGAAAGAAGGGAATTTGCAAAAAAAAAAAAAAAAAAA
AAAAAAA

FIGURE 34

MATEGAAQLGNRVAGMVCSLWVLLLVSSVLALEEVLLDTTGETSEIGWLTYPPGGWDEVS
VLDDQRRLTRTFEACHVAGAPPGTGQDNWLQTHFVERRGAQRAHIRLHFSVRACSSLGVS
GGTCRETFTLYYRQAEEPDSPDSVSSWHLKRWTKVDTIAADESFPSSSSSSSSSSSSAAW
AVGPHGAGQRAGLQLNVKERSFGPLTQRGFYVAFQDTGACLALVAVRLFSYTCPAVLRSF
ASFPETQASGAGGASLVAAVGTCVAHAEPEEDGVGGQAGGSPPRLHCNGEGKWMVAVGGC
RCQPGYQPARGDKACQACPRGLYKASAGNAPCSPCPARSHAPNPAAPVCPCLEGFYRASS
DPPEAPCTGPPSAPQELWFEVQGSALMLHWRLPRELGGRGDLLFNVVCKECEGRQEPASG
GGGTCHRCRDEVHFDPRQRGLTESRVLVGGLRAHVPYILEVQAVNGVSELSPDPPQAAAI
NVSTSHEVPSAVPVVHQVSRASNSITVSWPQPDQTNGNILDYQLRYYDQAEDESHSFTLT
SETNTATVTQLSPGHIYGFQVRARTAAGHGPYGGKVYFQTLPQGELSSQLPERLSLVIGS
TLGALAFLLLAAITVLAVVFQRKRRGTGYTEQLQQYSSPGLGVKYYIDPSTYEDPCQAIR
ELAREVDPAYIKIEEVIGTGSFGEVRQGRLQPRGRREQTVAIQALWAGGAESLQMTFLGR
AAVLGQFQHPNILRLEGVVTKSRPLMVLTEFMELGPLDSFLRQREGQFSSLQLVAMQRGV
AAAMQYLSSFAFVHRSLSAHSVLVNSHLVCKVARLGHSPQGPSCLLRWAAPEVIAHGKHT
HVGSDELWRTALLGHE

signal sequence:
Amino acids 1-31

Transmembrane domains:
Amino acids 217-234;598-618

N-glycosylation site:
Amino acids 481-485

Glycosaminoglycan attachment sites:
Amino acids 249-253;419-423

cAMP- and cGMP-dependent protein kinase phosphorylation sites:
Amino acids 66-70;150-154;624-628

Tyrosine kinase phosphorylation sites:
Amino acids 644-673;664-671

N-myristoylation sites:
Amino acids 10-16;15-21;79-85;99-105;118-124;188-194;192-198;218-224;250-256;261-267;275-281;276-282;298-304;321-327;328-334;420-426;421-427;440-446;449-455;599-605;626-632;708-714;766-772;779-785

Amidation site:
Amino acids 693-697

Cell attachment sequences:
Amino acids 310-313;399-402

FIGURE 35

GGGGTCTCCCTCAGGGCCGGGAGGCACAGCGGTCCCTGCTTGCTGAAGGGCTGGATGTAC
GCATCCGCAGGTTCCCGCGGACTTGGGGGCGCCCGCTGAGCCCCGGCGCCCGCAGAAGAC
TTGTGTTTGCCTCCTGCAGCCTCAACCCGGAGGGCAGCGAGGGCCTACCACC**ATG**ATCAC
TGGTGTGTTCAGCATGCGCTTGTGGACCCCAGTGGGCGTCCTGACCTCGCTGGCGTACTG
CCTGCACCAGCGGCGGGTGGCCCTGGCCGAGCTGCAGGAGGCCGATGGCCAGTGTCCGGT
CGACCGCAGCCTGCTGAAGTTGAAAATGGTGCAGGTCGTGTTTCGACACGGGGCTCGGAG
TCCTCTCAAGCCGCTCCCGCTGGAGGAGCAGGTAGAGTGGAACCCCCAGCTATTAGAGGT
CCCACCCCAAACTCAGTTTGATTACACAGTCACCAATCTAGCTGGTGGTCCGAAACCATA
TTCTCCTTACGACTCTCAATACCATGAGACCACCCTGAAGGGGGGCATGTTTGCTGGGCA
GCTGACCAAGGTGGGCATGCAGCAAATGTTTGCCTTGGGAGAGAGACTGAGGAAGAACTA
TGTGGAAGACATTCCCTTTCTTTCACCAACCTTCAACCCACAGGAGGTCTTTATTCGTTC
CACTAACATTTTTCGGAATCTGGAGTCCACCCGTTGTTTGCTGGCTGGGCTTTTCCAGTG
TCAGAAAGAAGGACCCATCATCATCCACACTGATGAAGCAGATTCAGAAGTCTTGTATCC
CAACTACCAAAGCTGCTGGAGCCTGAGGCAGAGAACCAGAGGCCGGAGGCAGACTGCCTC
TTTACAGCCAGGAATCTCAGAGGATTTGAAAAAGGTGAAGGACAGGATGGGCATTGACAG
TAGTGATAAAGTGGACTTCTTCATCCTCCTGGACAACGTGGCTGCCGAGCAGGCACACAA
CCTCCCAAGCTGCCCCATGCTGAAGAGATTTGCACGGATGATCGAACAGAGAGCTGTGGA
CACATCCTTGTACATACTGCCCAAGGAAGACAGGGAAAGTCTTCAGATGGCAGTAGGCCC
ATTCCTCCACATCCTAGAGAGCAACCTGCTGAAAGCCATGGACTCTGCCACTGCCCCCGA
CAAGATCAGAAAGCTGTATCTCTATGCGGCTCATGATGTGACCTTCATACCGCTCTTAAT
GACCCTGGGGATTTTTGACCACAAATGGCCACCGTTTGCTGTTGACCTGACCATGGAACT
TTACCAGCACCTGGAATCTAAGGAGTGGTTTGTGCAGCTCTATTACCACGGGAAGGAGCA
GGTGCCGAGAGGTTGCCCTGATGGGCTCTGCCCGCTGGACATGTTCTTGAATGCCATGTC
AGTTTATACCTTAAGCCCAGAAAAATACCATGCACTCTGCTCTCAAACTCAGGTGATGGA
AGTTGGAAATGAAGAG**TAA**CTGATTTATAAAAGCAGGATGTGTTGATTTTAAAATAAAGT
GCCTTTATACAATG

FIGURE 36

MITGVFSMRLWTPVGVLTSLAYCLHQRRVALAELQEADGQCPVDRSLLKLKMVQVVFRHG
ARSPLKPLPLEEQVEWNPQLLEVPPQTQFDYTVTNLAGGPKPYSPYDSQYHETTLKGGMF
AGQLTKVGMQQMFALGERLRKNYVEDIPFLSPTFNPQEVFIRSTNIFRNLESTRCLLAGL
FQCQKEGPIIIHTDEADSEVLYPNYQSCWSLRQRTRGRRQTASLQPGISEDLKKVKDRMG
IDSSDKVDFFILLDNVAAEQAHNLPSCPMLKRFARMIEQRAVDTSLYILPKEDRESLQMA
VGPFLHILESNLLKAMDSATAPDKIRKLYLYAAHDVTFIPLLMTLGIFDHKWPPFAVDLT
MELYQHLESKEWFVQLYYHGKEQVPRGCPDGLCPLDMFLNAMSVYTLSPEKYHALCSQTQ
VMEVGNEE

Signal sequence:
amino acids 1-23

cAMP- and cGMP-dependent protein kinase phosphorylation site:
amino acids 218-222

Casein kinase II phosphorylation site:
amino acids 87-91, 104-108, 320-324

Tyrosine kinase phosphorylation site:
amino acids 280-288

N-myristoylation site:
amino acids 15-21, 117-123, 118-124, 179-185, 240-246, 387-393

Amidation site:
amino acids 216-220

Leucine zipper pattern:
amino acids 10-32

Histidine acid phosphatases phosphohistidine signature:
amino acids 50-65

FIGURE 37

ACTGCACTCGGTTCTATCGATTGAATTCCCCGGGGATCCTCTAGAGATCCCTCGACCTCG
ACCCACGCGTCCGCGGACGCGTGGGCGGACGCGTGGGCCGGCTACCAGGAAGAGTCTGCC
GAAGGTGAAGGCC<u>ATG</u>GACTTCATCACCTCCACAGCCATCCTGCCCCTGCTGTTCGGCTG
CCTGGGCGTCTTCGGCCTCTTCCGGCTGCTGCAGTGGGTGCGCGGGAAGGCCTACCTGCG
GAATGCTGTGGTGGTGATCACAGGCGCCACCTCAGGGCTGGGCAAAGAATGTGCAAAAGT
CTTCTATGCTGCGGGTGCTAAACTGGTGCTCTGTGGCCGGAATGGTGGGGCCCTAGAAGA
GCTCATCAGAGAACTTACCGCTTCTCATGCCACCAAGGTGCAGACACACAAGCCTTACTT
GGTGACCTTCGACCTCACAGACTCTGGGGCCATAGTTGCAGCAGCAGCTGAGATCCTGCA
GTGCTTTGGCTATGTCGACATACTTGTCAACAATGCTGGGATCAGCTACCGTGGTACCAT
CATGGACACCACAGTGGATGTGGACAAGAGGGTCATGGAGACAAACTACTTTGGCCCAGT
TGCTCTAACGAAAGCACTCCTGCCCTCCATGATCAAGAGGAGGCAAGGCCACATTGTCGC
CATCAGCAGCATCCAGGGCAAGATGAGCATTCCTTTTCGATCAGCATATGCAGCCTCCAA
GCACGCAACCCAGGCTTTCTTTGACTGTCTGCGTGCCGAGATGGAACAGTATGAAATTGA
GGTGACCGTCATCAGCCCCGGCTACATCCACACCAACCTCTCTGTAAATGCCATCACCGC
GGATGGATCTAGGTATGGAGTTATGGACACCACCACAGCCCAGGGCCGAAGCCCTGTGGA
GGTGGCCCAGGATGTTCTTGCTGCTGTGGGGAAGAAGAAGAAAGATGTGATCCTGGCTGA
CTTACTGCCTTCCTTGGCTGTTTATCTTCGAACTCTGGCTCCTGGGCTCTTCTTCAGCCT
CATGGCCTCCAGGGCCAGAAAAGAGCGGAAATCCAAGAACTCC<u>**TAG**</u>TACTCTGACCAGCC
AGGGCCAGGGCAGAGAAGCAGCACTCTTAGGCTTGCTTACTCTACAAGGGACAGTTGCAT
TTGTTGAGACTTTAATGGAGATTTGTCTCACAAGTGGGAAAGACTGAAGAAACACATCTC
GTGCAGATCTGCTGGCAGAGGACAATCAAAAACGACAACAAGCTTCTTCCCAGGGTGAGG
GGAAACACTTAAGGAATAAATATGGAGCTGGGGTTTAACACTAAAAACTAGAAATAAACA
TCTCAAACAGTAAAAAAAAAAAAAAAAGGGCGGCCGCGACTCTAGAGTCGACCTGCAGAAG
CTTGGCCGCCATGGCCCAACTTGTTTATTGCAGCTTATAATGGTTAC

FIGURE 38

MDFITSTAILPLLFGCLGVFGLFRLLQWVRGKAYLRNAVVVITGATSGLGKECAKVFYAA
GAKLVLCGRNGGALEELIRELTASHATKVQTHKPYLVTFDLTDSGAIVAAAAEILQCFGY
VDILVNNAGISYRGTIMDTTVDVDKRVMETNYFGPVALTKALLPSMIKRRQGHIVAISSI
QGKMSIPFRSAYAASKHATQAFFDCLRAEMEQYEIEVTVISPGYIHTNLSVNAITADGSR
YGVMDTTTAQGRSPVEVAQDVLAAVGKKKKDVILADLLPSLAVYLRTLAPGLFFSLMASR
ARKERKSKNS

Signal sequence:
amino acids 1-21

Transmembrane domain:
amino acids 104-120, 278-292

N-glycosylation site:
amino acids 228-232

Glycosaminoglycan attachment site:
amino acids 47-51

Casein kinase II phosphorylation site:
amino acids 135-139, 139-143, 253-257

Tyrosine kinase phosphorylation site:
amino acids 145-153, 146-153

N-myristoylation site:
amino acids 44-50, 105-111, 238-244, 242-248, 291-297

Amidation site:
amino acids 265-269

Prokaryotic membrane lipoprotein lipid attachment site:
amino acids 6-17

FIGURE 39

GCAAGCCAAGGCGCTGTTTGAGAAGGTGAAGAAGTTCCGGACCCATGTGGAGGAGGGGGACATTGT
GTACCGCCTCTAC**ATG**CGGCAGACCATCATCAAGGTGATCAAGTTCATCCTCATCATCTGCTACAC
CGTCTACTACGTGCACAACATCAAGTTCGACGTGGACTGCACCGTGGACATTGAGAGCCTGACGGG
CTACCGCACCTACCGCTGTGCCCACCCCCTGGCCACACTCTTCAAGATCCTGGCGTCCTTCTACAT
CAGCCTAGTCATCTTCTACGGCCTCATCTGCATGTACACACTGTGGTGGATGCTACGGCGCTCCCT
CAAGAAGTACTCGTTTGAGTCGATCCGTGAGGAGAGCAGCTACAGCGACATCCCCGACGTCAAGAA
CGACTTCGCCTTCATGCTGCACCTCATTGACCAATACGACCCGCTCTACTCCAAGCGCTTCGCCGT
CTTCCTGTCGGAGGTGAGTGAGAACAAGCTGCGGCAGCTGAACCTCAACAACGAGTGGACGCTGGA
CAAGCTCCGGCAGCGGCTCACCAAGAACGCGCAGGACAAGCTGGAGCTGCACCTGTTCATGCTCAG
TGGCATCCCTGACACTGTGTTTGACCTGGTGGAGCTGGAGGTCCTCAAGCTGGAGCTGATCCCCGA
CGTGACCATCCCGCCCAGCATTGCCCAGCTCACGGGCCTCAAGGAGCTGTGGCTCTACCACACAGC
GGCCAAGATTGAAGCGCCTGCGCTGGCCTTCCTGCGCGAGAACCTGCGGGCGCTGCACATCAAGTT
CACCGACATCAAGGAGATCCCGCTGTGGATCTATAGCCTGAAGACACTGGAGGAGCTGCACCTGAC
GGGCAACCTGAGCGCGGAGAACAACCGCTACATCGTCATCGACGGGCTGCGGGAGCTCAAACGCCT
CAAGGTGCTGCGGCTCAAGAGCAACCTAAGCAAGCTGCCACAGGTGGTCACAGATGTGGGCGTGCA
CCTGCAGAAGCTGTCCATCAACAATGAGGGCACCAAGCTCATCGTCCTCAACAGCCTCAAGAAGAT
GGCGAACCTGACTGAGCTGGAGCTGATCCGCTGCGACCTGGAGCGCATCCCCCACTCCATCTTCAG
CCTCCACAACCTGCAGGAGATTGACCTCAAGGACAACAACCTCAAGACCATCGAGGAGATCATCAG
CTTCCAGCACCTGCACCGCCTCACCTGCCTTAAGCTGTGGTACAACCACATCGCCTACATCCCCAT
CCAGATCGGCAACCTCACCAACCTGGAGCGCCTCTACCTGAACCGCAACAAGATCGAGAAGATCCC
CACCCAGCTCTTCTACTGCCGCAAGCTGCGCTACCTGGACCTCAGCCACAACAACCTGACCTTCCT
CCCTGCCGACATCGGCCTCCTGCAGAACCTCCAGAACCTAGCCATCACGGCCAACCGGATCGAGAC
GCTCCCTCCGGAGCTCTTCCAGTGCCGGAAGCTGCGGGCCCTGCACCTGGGCAACAACGTGCTGCA
GTCACTGCCCTCCAGGGTGGGCGAGCTGACCAACCTGACGCAGATCGAGCTGCGGGGCAACCGGCT
GGAGTGCCTGCCTGTGGAGCTGGGCGAGTGCCCACTGCTCAAGCGCAGCGGCTTGGTGGTGGAGGA
GGACCTGTTCAACACACTGCCACCCGAGGTGAAGGAGCGGCTGTGGAGGGCTGACAAGGAGCAGGC
C**TGA**GCGAGGCCGGCCCAGCACAGCAAGCAGCAGGACCGCTGCCCAGTCCTCAGGCCCGGAGGGGC
AGGCCTAGCTTCTCCCAGAACTCCCGGACAGCCAGGACAGCCTCGCGGCTGGGCAGGAGCCTGGGG
CCGCTTGTGAGTCAGGCCAGAGCGAGAGGACAGTATCTGTGGGGCTGGCCCCTTTTCTCCCTCTGA
GACTCACGTCCCCCAGGGCAAGTGCTTGTGGAGGAGAGCAAGTCTCAAGAGCGCAGTATTTGGATA
ATCAGGGTCTCCTCCCTGGAGGCCAGCTCTGCCCCAGGGGCTGAGCTGCCACCAGAGGTCCTGGGA
CCCTCACTTTAGTTCTTGGTATTTATTTTTCTCCATCTCCCACCTCCTTCATCCAGATAACTTATA
CATTCCCAAGAAAGTTCAGCCCAGATGGAAGGTGTTCAGGGAAAGGTGGGCTGCCTTTTCCCCTTG
TCCTTATTTAGCGATGCCGCCGGGCATTTAACACCCACCTGGACTTCAGCAGAGTGGTCCGGGGCG
AACCAGCCATGGGACGGTCACCCAGCAGTGCCGGGCTGGGCTCTGCGGTGCGGTCCACGGGAGAGC
AGGCCTCCAGCTGGAAAGGCCAGGCCTGGAGCTTGCCTCTTCAGTTTTTGTGGCAGTTTTAGTTTT
TTGTTTTTTTTTTTTTAATCAAAAAACAATTTTTTTAAAAAAAAGCTTTGAAAATGGATGGTTT
GGGTATTAAAAAGAAAAAAAAAACTTAAAAAAAAAAAGACACTAACGGCCAGTGAGTTGGAGTCTC
AGGGCAGGGTGGCAGTTTCCCTTGAGCAAAGCAGCCAGACGTTGAACTGTGTTTCCTTTCCCTGGG
CGCAGGGTGCAGGGTGTCTTCCGGATCTGGTGTGACCTTGGTCCAGGAGTTCTATTTGTTCCTGGG
GAGGGAGGTTTTTTTGTTTGTTTTTTGGGTTTTTTTGGTGTCTTGTTTTCTTTCTCCTCCATGTGT
CTTGGCAGGCACTCATTTCTGTGGCTGTCGGCCAGAGGGAATGTTCTGGAGCTGCCAAGGAGGGAG
GAGACTCGGGTTGGCTAATCCCCGGATGAACGGTGCTCCATTCGCACCTCCCCTCCTCGTGCCTGC
CCTGCCTCTCCACGCACAGTGTTAAGGAGCCAAGAGGAGCCACTTCGCCCAGACTTTGTTTCCCCA
CCTCCTGCGGCATGGGTGTGTCCAGTGCCACCGCTGGCCTCCGCTGCTTCCATCAGCCCTGTCGCC
ACCTGGTCCTTCATGAAGAGCAGACACTTAGAGGCTGGTCGGGAATGGGGAGGTCGCCCCTGGGAG
GGCAGGCGTTGGTTCCAAGCCGGTTCCCGTCCCTGGCGCCTGGAGTGCACACAGCCCAGTCGGCAC
CTGGTGGCTGGAAGCCAACCTGCTTTAGATCACTCGGGTCCCCACCTTAGAAGGGTCCCCGCCTTA
GATCAATCACGTGGACACTAAGGCACGTTTTAGAGTCTCTTGTCTTAATGATTATGTCCATCCGTC
TGTCCGTCCATTTGTGTTTTCTGCGTCGTGTCATTGGATATAATCCTCAGAAATAATGCACACTAG
CCTCTGACAACCATGAAGCAAAAATCCGTTACATGTGGGTCTGAACTTGTAGACTCGGTCACAGTA
TCAAATAAAATCTATAACAGAAAAAAAAAAAAAAA

FIGURE 40

MRQTIIKVIKFILIICYTVYYVHNIKFDVDCTVDIESLTGYRTYRCAHPLATLFKILASF
YISLVIFYGLICMYTLWWMLRRSLKKYSFESIREESSYSDIPDVKNDFAFMLHLIDQYDP
LYSKRFAVFLSEVSENKLRQLNLNNEWTLDKLRQRLTKNAQDKLELHLFMLSGIPDTVFD
LVELEVLKLELIPDVTIPPSIAQLTGLKELWLYHTAAKIEAPALAFLRENLRALHIKFTD
IKEIPLWIYSLKTLEELHLTGNLSAENNRYIVIDGLRELKRLKVLRLKSNLSKLPQVVTD
VGVHLQKLSINNEGTKLIVLNSLKKMANLTELELIRCDLERIPHSIFSLHNLQEIDLKDN
NLKTIEEIISFQHLHRLTCLKLWYNHIAYIPIQIGNLTNLERLYLNRNKIEKIPTQLFYC
RKLRYLDLSHNNLTFLPADIGLLQNLQNLAITANRIETLPPELFQCRKLRALHLGNNVLQ
SLPSRVGELTNLTQIELRGNRLECLPVELGECPLLKRSGLVVEEDLFNTLPPEVKERLWR
ADKEQA

Transmembrane domain:
amino acids 51-75 (type II)

N-glycosylation site:
amino acids 262-266, 290-294, 328-332, 396-400, 432-436, 491-495

cAMP- and cGMP-dependent protein kinase phosphorylation site:
amino acids 85-89

Casein kinase II phosphorylation site:
amino acids 91-95, 97-101, 177-181, 253-257, 330-334, 364-368, 398-402, 493-497

N-myristoylation site:
amino acids 173-179, 261-267, 395-401, 441-447

FIGURE 41

GGGGGAGAAGGCGGCCGAGCCCCAGCTCTCCGAGCACCGGGTCGGAAGCCGCGACCCGAG
CCGCGCAGGAAGCTGGGACCGGAACCTCGGCGGACCCGGCCCCACCCAACTCACCTGCGC
AGGTCACCAGCACCCTCGGAACCCAGAGGCCCGCGCTCTGAAGGTGACCCCCCTGGGGAG
GAAGGCGATGGCCCCTGCGAGGACGATGGCCCGCGCCCGCCTCGCCCCGGCCGGCATCCC
TGCCGTCGCCTTGTGGCTTCTGTGCACGCTCGGCCTCCAGGGCACCCAGGCCGGGCCACC
GCCCGCGCCCCCTGGGCTGCCCGCGGGAGCCGACTGCCTGAACAGCTTTACCGCCGGGGT
GCCTGGCTTCGTGCTGGACACCAACGCCTCGGTCAGCAACGGAGCTACCTTCCTGGAGTC
CCCCACCGTGCGCCGGGGCTGGGACTGCGTGCGCGCCTGCTGCACCACCCAGAACTGCAA
CTTGGCGCTAGTGGAGCTGCAGCCCGACCGCGGGGAGGACGCCATCGCCGCCTGCTTCCT
CATCAACTGCCTCTACGAGCAGAACTTCGTGTGCAAGTTCGCGCCCAGGGAGGGCTTCAT
CAACTACCTCACGAGGGAAGTGTACCGCTCCTACCGCCAGCTGCGGACCCAGGGCTTTGG
AGGGTCTGGGATCCCCAAGGCCTGGGCAGGCATAGACTTGAAGGTACAACCCCAGGAACC
CCTGGTGCTGAAGGATGTGGAAAACACAGATTGGCGCCTACTGCGGGGTGACACGGATGT
CAGGGTAGAGAGGAAAGACCCAAACCAGGTGGAACTGTGGGGACTCAAGGAAGGCACCTA
CCTGTTCCAGCTGACAGTGACTAGCTCAGACCACCCAGAGGACACGGCCAACGTCACAGT
CACTGTGCTGTCCACCAAGCAGACAGAAGACTACTGCCTCGCATCCAACAAGGTGGGTCG
CTGCCGGGGCTCTTTCCCACGCTGGTACTATGACCCCACGGAGCAGATCTGCAAGAGTTT
CGTTTATGGAGGCTGCTTGGGCAACAAGAACAACTACCTTCGGGAAGAAGAGTGCATTCT
AGCCTGTCGGGGTGTGCAAGGTGGGCCTTTGAGAGGCAGCTCTGGGGCTCAGGCGACTTT
CCCCCAGGGCCCCTCCATGGAAAGGCGCCATCCAGTGTGCTCTGGCACCTGTCAGCCCAC
CCAGTTCCGCTGCAGCAATGGCTGCTGCATCGACAGTTTCCTGGAGTGTGACGACACCCC
CAACTGCCCCGACGCCTCCGACGAGGCTGCCTGTGAAAAATACACGAGTGGCTTTGACGA
GCTCCAGCGCATCCATTTCCCCAGTGACAAAGGGCACTGCGTGGACCTGCCAGACACAGG
ACTCTGCAAGGAGAGCATCCCGCGCTGGTACTACAACCCCTTCAGCGAACACTGCGCCCG
CTTTACCTATGGTGGTTGTTATGGCAACAAGAACAACTTTGAGGAAGAGCAGCAGTGCCT
CGAGTCTTGTCGCGGCATCTCCAAGAAGGATGTGTTTGGCCTGAGGCGGGAAATCCCCAT
TCCCAGCACAGGCTCTGTGGAGATGGCTGTCACAGTGTTCCTGGTCATCTGCATTGTGGT
GGTGGTAGCCATCTTGGGTTACTGCTTCTTCAAGAACCAGAGAAAGGACTTCCACGGACA
CCACCACCACCCACCACCCACCCCTGCCAGCTCCACTGTCTCCACTACCGAGGACACGGA
GCACCTGGTCTATAACCACACCACCCGGCCCCTCTGAGCCTGGGTCTCACCGGCTCTCAC
CTGGCCCTGCTTCCTGCTTGCCAAGGCAGAGGCCTGGGCTGGGAAAAACTTTGGAACCAG
ACTCTTGCCTGTTTCCCAGGCCCACTGTGCCTCAGAGACCAGGGCTCCAGCCCCTCTTGG
AGAAGTCTCAGCTAAGCTCACGTCCTGAGAAAGCTCAAAGGTTTGGAAGGAGCAGAAAAC
CCTTGGGCCAGAAGTACCAGACTAGATGGACCTGCCTGCATAGGAGTTTGGAGGAAGTTG
GAGTTTTGTTTCCTCTGTTCAAAGCTGCCTGTCCCTACCCCATGGTGCTAGGAAGAGGAG
TGGGGTGGTGTCAGACCCTGGAGGCCCCAACCCTGTCCTCCCGAGCTCCTCTTCCATGCT
GTGCGCCCAGGGCTGGGAGGAAGGACTTCCCTGTGTAGTTTGTGCTGTAAAGAGTTGCTT
TTTGTTTATTTAATGCTGTGGCATGGGTGAAGAGGAGGGGAAGAGGCCTGTTTGGCCTCT
CTGTCCTCTCTTCCTCTTCCCCCAAGATTGAGCTCTCTGCCCTTGATCAGCCCCACCCTG
GCCTAGACCAGCAGACAGAGCCAGGAGAGGCTCAGCTGCATTCCGCAGCCCCCACCCCCA
AGGTTCTCCAACATCACAGCCCAGCCCACCCACTGGGTAATAAAAGTGGTTTGTGGAAAA
AAAAAAAAAAAAAAAAAAAAAA

FIGURE 42

MAPARTMARARLAPAGIPAVALWLLCTLGLQGTQAGPPPAPPGLPAGADCLNSFTAGVPG
FVLDTNASVSNGATFLESPTVRRGWDCVRACCTTQNCNLALVELQPDRGEDAIAACFLIN
CLYEQNFVCKFAPREGFINYLTREVYRSYRQLRTQGFGGSGIPKAWAGIDLKVQPQEPLV
LKDVENTDWRLLRGDTDVRVERKDPNQVELWGLKEGTYLFQLTVTSSDHPEDTANVTVTV
LSTKQTEDYCLASNKVGRCRGSFPRWYYDPTEQICKSFVYGGCLGNKNNYLREEECILAC
RGVQGGPLRGSSGAQATFPQGPSMERRHPVCSGTCQPTQFRCSNGCCIDSFLECDDTPNC
PDASDEAACEKYTSGFDELQRIHFPSDKGHCVDLPDTGLCKESIPRWYYNPFSEHCARFT
YGGCYGNKNNFEEEQQCLESCRGISKKDVFGLRREIPIPSTGSVEMAVTVFLVICIVVVV
AILGYCFFKNQRKDFHGHHHHPPPTPASSTVSTTEDTEHLVYNHTTRPL

signal sequence:
Amino acids 1-35

transmembrane domain:
Amino acids 466-483

N-glycosylation sites:
Amino acids 66-70;235-239;523-527

N-myristoylation sites:
Amino acids
29-35;43-49;161-167;212-218;281-287;282-288;285-291;
310-316;313-319;422-428;423-429;426-432

Cell attachment sequence:
Amino acids 193-199

Pancreatic trypsin inhibitor (Kunitz) family signatures:
Amino acids 278-298;419-438

FIGURE 43

CCCACGCGTCCGCACCTCGGCCCCGGGCTCCGAAGCGGCTCGGGGGCGCCCTTTCGGTCA
ACATCGTAGTCCACCCCCTCCCCATCCCCAGCCCCCGGGGATTCAGGCTCGCCAGCGCCC
AGCCAGGGAGCCGGCCGGGAAGCGCG**<u>ATG</u>**GGGGCCCCAGCCGCCTCGCTCCTGCTCCTGC
TCCTGCTGTTCGCCTGCTGCTGGGCGCCCGGCGGGGCCAACCTCTCCCAGGACGACAGCC
AGCCCTGGACATCTGATGAAACAGTGGTGGCTGGTGGCACCGTGGTGCTCAAGTGCCAAG
TGAAAGATCACGAGGACTCATCCCTGCAATGGTCTAACCCTGCTCAGCAGACTCTCTACT
TTGGGGAGAAGAGAGCCCTTCGAGATAATCGAATTCAGCTGGTTACCTCTACGCCCCACG
AGCTCAGCATCAGCATCAGCAATGTGGCCCTGGCAGACGAGGGCGAGTACACCTGCTCAA
TCTTCACTATGCCTGTGCGAACTGCCAAGTCCCTCGTCACTGTGCTAGGAATTCCACAGA
AGCCCATCATCACTGGTTATAAATCTTCATTACGGGAAAAAGACACAGCCACCCTAAACT
GTCAGTCTTCTGGGAGCAAGCCTGCAGCCCGGCTCACCTGGAGAAAGGGTGACCAAGAAC
TCCACGGAGAACCAACCCGCATACAGGAAGATCCCAATGGTAAAACCTTCACTGTCAGCA
GCTCGGTGACATTCCAGGTTACCCGGGAGGATGATGGGGCGAGCATCGTGTGCTCTGTGA
ACCATGAATCTCTAAAGGGAGCTGACAGATCCACCTCTCAACGCATTGAAGTTTTATACA
CACCAACTGCGATGATTAGGCCAGACCCTCCCCATCCTCGTGAGGGCCAGAAGCTGTTGC
TACACTGTGAGGGTCGCGGCAATCCAGTCCCCCAGCAGTACCTATGGGAGAAGGAGGGCA
GTGTGCCACCCCTGAAGATGACCCAGGAGAGTGCCCTGATCTTCCCTTTCCTCAACAAGA
GTGACAGTGGCACCTACGGCTGCACAGCCACCAGCAACATGGGCAGCTACAAGGCCTACT
ACACCCTCAATGTTAATGACCCCAGTCCGGTGCCCTCCTCCTCCAGCACCTACCACGCCA
TCATCGGTGGGATCGTGGCTTTCATTGTCTTCCTGCTGCTCATCATGCTCATCTTCCTTG
GCCACTACTTGATCCGGCACAAAGGAACCTACCTGACACATGAGGCAAAAGGCTCCGACG
ATGCTCCAGACGCGGACACGGCCATCATCAATGCAGAAGGCGGGCAGTCAGGAGGGGACG
ACAAGAAGGAATATTTCATC**<u>TAG</u>**AGGCGCCTGCCCACTTCCTGCGCCCCCCAGGGGCCCT
GTGGGGACTGCTGGGGCCGTCACCAACCCGGACTTGTACAGAGCAACCGCAGGGCCGCCC
CTCCCGCTTGCTCCCCAGCCCACCCACCCCCCTGTACAGAATGTCTGCTTTGGGTGCGGT
TTTGTACTCGGTTTGGAATGGGGAGGGAGGAGGGCGGGGGAGGGGAGGGTTGCCCTCAG
CCCTTTCCGTGGCTTCTCTGCATTTGGGTTATTATTATTTTTGTAACAATCCCAAATCAA
ATCTGTCTCCAGGCTGGAGAGGCAGGAGCCCTGGGGTGAGAAAAGCAAAAAACAAACAAA
AAACA

FIGURE 44

MGAPAASLLLLLLLFACCWAPGGANLSQDDSQPWTSDETVVAGGTVVLKCQVKDHEDSSL
QWSNPAQQTLYFGEKRALRDNRIQLVTSTPHELSISISNVALADEGEYTCSIFTMPVRTA
KSLVTVLGIPQKPIITGYKSSLREKDTATLNCQSSGSKPAARLTWRKGDQELHGEPTRIQ
EDPNGKTFTVSSSVTFQVTREDDGASIVCSVNHESLKGADRSTSQRIEVLYTPTAMIRPD
PPHPREGQKLLLHCEGRGNPVPQQYLWEKEGSVPPLKMTQESALIFPFLNKSDSGTYGCT
ATSNMGSYKAYYTLNVNDPSPVPSSSSTYHAIIGGIVAFIVFLLLIMLIFLGHYLIRHKG
TYLTHEAKGSDDAPDADTAIINAEGGQSGGDDKKEYFI

Signal sequence:
amino acids 1-20

Transmembrane domain:
amino acids 331-352

N-glycosylation site:
amino acids 25-29, 290-294

Casein kinase II phosphorylation site:
amino acids 27-31, 35-39, 89-93, 141-145, 199-203, 388-392

N-myristoylation site:
amino acids 2-8, 23-29, 156-162, 218-224, 295-301, 298-304, 306-310, 334-340, 360-364, 385-389, 386-390

Prokaryotic membrane lipoprotein lipid attachment site:
amino acids 7-18

FIGURE 45

ACTTGCCATCACCTGTTGCCAGTGTGGAAAAATTCTCCCTGTTGAATTTTTGCACATGG
AGGACAGCAGCAAAGAGGGCAACACAGGCTGATAAGACCAGAGACAGCAGGGAGATTATT
TTACCATACGCCCTCAGGACGTTCCCTCTAGCTGGAGTTCTGGACTTCAACAGAACCCCA
TCCAGTCATTTTGATTTTGCTGTTTATTTTTTTTTTCTTTTTCTTTTTCCCACCACATTG
TATTTTATTTCCGTACTTCAGAA**ATG**GGCCTACAGACCACAAAGTGGCCCAGCCATGGGG
CTTTTTTCCTGAAGTCTTGGCTTATCATTTCCCTGGGGCTCTACTCACAGGTGTCCAAAC
TCCTGGCCTGCCCTAGTGTGTGCCGCTGCGACAGGAACTTTGTCTACTGTAATGAGCGAA
GCTTGACCTCAGTGCCTCTTGGGATCCCGGAGGGCGTAACCGTACTCTACCTCCACAACA
ACCAAATTAATAATGCTGGATTTCCTGCAGAACTGCACAATGTACAGTCGGTGCACACGG
TCTACCTGTATGGCAACCAACTGGACGAATTCCCCATGAACCTTCCCAAGAATGTCAGAG
TTCTCCATTTGCAGGAAAACAATATTCAGACCATTTCACGGGCTGCTCTTGCCCAGCTCT
TGAAGCTTGAAGAGCTGCACCTGGATGACAACTCCATATCCACAGTGGGGGTGGAAGACG
GGGCCTTCCGGGAGGCTATTAGCCTCAAATTGTTGTTTTTGTCTAAGAATCACCTGAGCA
GTGTGCCTGTTGGGCTTCCTGTGGACTTGCAAGAGCTGAGAGTGGATGAAAATCGAATTG
CTGTCATATCCGACATGGCCTTCCAGAATCTCACGAGCTTGGAGCGTCTTATTGTGGACG
GGAACCTCCTGACCAACAAGGGTATCGCCGAGGGCACCTTCAGCCATCTCACCAAGCTCA
AGGAATTTTCAATTGTACGTAATTCGCTGTCCCACCCTCCTCCCGATCTCCCAGGTACGC
ATCTGATCAGGCTCTATTTGCAGGACAACCAGATAAACCACATTCCTTTGACAGCCTTCT
CAAATCTGCGTAAGCTGGAACGGCTGGATATATCCAACAACCAACTGCGGATGCTGACTC
AAGGGGTTTTTGATAATCTCTCCAACCTGAAGCAGCTCACTGCTCGGAATAACCCTTGGT
TTTGTGACTGCAGTATTAAATGGGTCACAGAATGGCTCAAATATATCCCTTCATCTCTCA
ACGTGCGGGGTTTCATGTGCCAAGGTCCTGAACAAGTCCGGGGGATGGCCGTCAGGGAAT
TAAATATGAATCTTTTGTCCTGTCCCACCACGACCCCCGGCCTGCCTCTCTTCACCCCAG
CCCCAAGTACAGCTTCTCCGACCACTCAGCCTCCCACCCTCTCTATTCCAAACCCTAGCA
GAAGCTACACGCCTCCAACTCCTACCACATCGAAACTTCCCACGATTCCTGACTGGGATG
GCAGAGAAAGAGTGACCCCACCTATTTCTGAACGGATCCAGCTCTCTATCCATTTTGTGA
ATGATACTTCCATTCAAGTCAGCTGGCTCTCTCTCTTCACCGTGATGGCATACAAACTCA
CATGGGTGAAAATGGGCCACAGTTTAGTAGGGGGCATCGTTCAGGAGCGCATAGTCAGCG
GTGAGAAGCAACACCTGAGCCTGGTTAACTTAGAGCCCCGATCCACCTATCGGATTTGTT
TAGTGCCACTGGATGCTTTTAACTACCGCGCGGTAGAAGACACCATTTGTTCAGAGGCCA
CCACCCATGCCTCCTATCTGAACAACGGCAGCAACACAGCGTCCAGCCATGAGCAGACGA
CGTCCCACAGCATGGGCTCCCCCTTTCTGCTGGCGGGCTTGATCGGGGGCGCGGTGATAT
TTGTGCTGGTGGTCTTGCTCAGCGTCTTTTGCTGGCATATGCACAAAAAGGGGCGCTACA
CCTCCCAGAAGTGGAAATACAACCGGGGCCGGCGGAAAGATGATTATTGCGAGGCAGGCA
CCAAGAAGGACAACTCCATCCTGGAGATGACAGAAACCAGTTTTCAGATCGTCTCCTTAA
ATAACGATCAACTCCTTAAAGGAGATTTCAGACTGCAGCCCATTTACACCCCAAATGGGG
GCATTAATTACACAGACTGCCATATCCCCAACAACATGCGATACTGCAACAGCAGCGTGC
CAGACCTGGAGCACTGCCATACG**TGA**CAGCCAGAGGCCCAGCGTTATCAAGGCGGACAAT
TAGACTCTTGAGAACACACTCGTGTGTGCACATAAAGACACGCAGATTACATTTGATAAA
TGTTACACAGATGCATTTGTGCATTTGAATACTCTGTAATTTATACGGTGTACTATATAA
TGGGATTTAAAAAAAGTGCTATCTTTTCTATTTCAAGTTAATTACAAACAGTTTTGTAAC
TCTTTGCTTTTTAAATCTT

FIGURE 46

MGLQTTKWPSHGAFFLKSWLIISLGLYSQVSKLLACPSVCRCDRNFVYCNERSLTSVPLG
IPEGVTVLYLHNNQINNAGFPAELHNVQSVHTVYLYGNQLDEFPMNLPKNVRVLHLQENN
IQTISRAALAQLLKLEELHLDDNSISTVGVEDGAFREAISLKLLFLSKNHLSSVPVGLPV
DLQELRVDENRIAVISDMAFQNLTSLERLIVDGNLLTNKGIAEGTFSHLTKLKEFSIVRN
SLSHPPPDLPGTHLIRLYLQDNQINHIPLTAFSNLRKLERLDISNNQLRMLTQGVFDNLS
NLKQLTARNNPWFCDCSIKWVTEWLKYIPSSLNVRGFMCQGPEQVRGMAVRELNMNLLSC
PTTTPGLPLFTPAPSTASPTTQPPTLSIPNPSRSYTPPTPTTSKLPTIPDWDGRERVTPP
ISERIQLSIHFVNDTSIQVSWLSLFTVMAYKLTWVKMGHSLVGGIVQERIVSGEKQHLSL
VNLEPRSTYRICLVPLDAFNYRAVEDTICSEATTHASYLNNGSNTASSHEQTTSHSMGSP
FLLAGLIGGAVIFVLVVLLSVFCWHMHKKGRYTSQKWKYNRGRRKDDYCEAGTKKDNSIL
EMTETSFQIVSLNNDQLLKGDFRLQPIYTPNGGINYTDCHIPNNMRYCNSSVPDLEHCHT

Signal peptide:
amino acids 1-42

Transmembrane domain:
amino acids 542-561

N-glycosylation site:
amino acids 202-206, 298-302, 433-437, 521-525, 635-639, 649-653

Casein kinase II phosphorylation site:
amino acids 204-208, 407-411, 527-531, 593-597, 598-602, 651-655

Tyrosine kinase phosphorylation site:
amino acids 319-328

N-myristoylation site:
amino acids 2-8, 60-66, 149-155, 213-219, 220-226, 294-300, 522-528, 545-551, 633-639

Amidation site:
amino acids 581-585

Leucine zipper pattern:
amino acids 164-186

Phospholipase A2 aspartic acid active site:
amino acids 39-50

FIGURE 47

GCAGCGAGCGCCGGGTGCGGCCCTGCCGCCGCAGGGATGTGACCTTCACCGTCGCTTAGC
CAGGATGACCGGAGCCCGTGTCTCGCGGCGTCCGCGCCTCGCTTCAGCCTCCCGGGTGCT
CTGACCGCACGCTCCCGGCTGCTAGGCTCCCCGGCACCGGCCTCGCC**ATG**CCGCCACCGC
CCGGGCCCGCCGCCGCCCTGGGCACTGCGCTTCTGCTGCTCCTGCTGGCTTCCGAGTCTT
CTCACACTGTGCTGTTGCGGGCGCGTGAGGCGGCGCAGTTTCTGCGGCCCAGGCAGCGCC
GCGCCTACCAAGTCTTCGAGGAGGCCAAGCAGGGCCACCTGGAACGGGAGTGCGTGGAGG
AGGTGTGCAGCAAAGAGGAGGCCAGAGAGGTGTTCGAGAACGACCCCGAGACGGAGTATT
TCTATCCACGATATCAAGAGTGCATGAGAAAATATGGCAGGCCTGAAGAAAAAAACCCAG
ATTTCGCCAAATGTGTTCAGAACTTGCCTGACCAGTGCACCCCAAACCCTTGTGATAAGA
AGGGTACTCATATCTGCCAAGACCTCATGGGCAACTTCTTCTGCGTGTGCACAGATGGCT
GGGGAGGCCGGCTCTGTGACAAAGATGTCAATGAGTGTGTCCAGAAGAATGGGGGCTGCA
GCCAGGTCTGCCACAACAAACCAGGAAGCTTCCAATGTGCCTGCCATAGTGGCTTCTCGC
TTGCATCAGACGGCCAGACCTGCCAAGATATCGATGAATGCACAGACTCAGACACCTGTG
GGGACGCGCGATGCAAGAACTTGCCAGGCTCCTACTCTTGCCTCTGCGATGAGGGATATA
CATACAGCTCCAAGGAGAAGACCTGCCAAGATGTGGACGAGTGCCAGCAGGATCGCTGTG
AGCAGACCTGTGTCAACTCCCCAGGCAGCTATACCTGCCACTGTGATGGGCGAGGGGGCC
TAAAACTATCCCCAGACATGGATACTTGTGAGGACATCTTACCATGTGTGCCCTTCAGCA
TGGCCAAGAGCGTGAAGTCCTTGTACCTGGGCCGCATGTTCAGCGGGACCCCCGTGATTA
GACTACGCTTCAAGAGGCTTCAGCCTACCAGGCTGCTGGCTGAATTTGACTTCCGCACTT
TTGACCCTGAAGGAGTCCTCTTCTTCGCTGGAGGCCGTTCAGACAGCACCTGGATTGTCC
TGGGCCTAAGAGCTGGGCGGCTTGAGCTGCAGCTTCGGTACAATGGCGTTGGGCGCATCA
CCAGCAGCGGGCCAACCATCAACCACGGCATGTGGCAAACTATCTCCGTGGAAGAGCTGG
AACGTAACCTTGTCATCAAGGTCAACAAAGATGCTGTAATGAAGATCGCGGTAGCTGGGG
AGCTGTTTCAGCTGGAGAGGGGCCTCTATCACCTGAATCTCACCGTGGGCGGCATTCCCT
TCAAGGAGAGTGAGCTCGTCCAGCCGATTAACCCTCGCCTGGATGGGTGCATGAGGAGTT
GGAACTGGCTGAACGGGGAAGACAGCGCCATCCAGGAGACAGTCAAGGCAAACACAAAAA
TGCAGTGCTTCTCTGTGACAGAAAGGGGCTCCTTCTTCCCGGGGAATGGATTTGCTACCT
ACAGGCTCAACTACACCCGAACATCGCTGGATGTCGGCACGGAAACCACCTGGGAAGTTA
AAGTTGTGGCTCGGATCCGCCCTGCCACGGACACGGGGGTGCTGCTGGCGCTGGTGGGGG
ACGACGATGTCGTCATCTCTGTGGCCCTAGTCGACTACCACTCTACAAAGAAGCTCAAGA
AGCAGTTGGTGGTCCTGGCAGTTGAGGATGTTGCCCTGGCACTGATGGAAATCAAGGTGT
GCGACAGCCAGGAACACACGGTCACTGTCTCCCTGCGGGAGGGTGAGGCCACCCTAGAAG
TGGATGGCACAAAGGGCCAGAGTGAAGTGAGCACTGCCCAGCTGCAGGAGCGACTGGACA
CACTTAAGACACATCTGCAAGGCTCTGTGCACACCTATGTTGGAGGCCTGCCAGAAGTAT
CGGTGATTTCTGCACCCGTCACTGCGTTCTACCGCGGATGCATGACTCTGGAGGTAAACG
GGAAAATCCTGGACCTGGATACGGCCTCGTACAAGCACAGTGACATCACCTCCCACTCCT
GCCCGCCTGTGGAGCATGCCACCCCC**TAG**ACCGAGCTGCAAGAGGGCTCCACACCTAAAG
ACAAAAATGAAGCAGGGTTTGGACACACAGCACTGGCTCCTCTCGCATGGTCCTGCAACA
CTGGAGCAGCGTGGACCGCCCTTGTGGTTTTTTTTCTTGAGATCTTTCTTTTTGCCTTG
TAACATATCTGTACATAATGGACGGGTGTCGGGTCACCGGCTGCTCAGAGAGAGCCACGT
GACCTGGTGGGAGCTGGCTGGAAGGGGCTGGGCTAGAGGGGCTGGCAGTTTGCAGCAGAA
CGGATGTGAAGAAAATAATTCTCTATTATTTTATTACTACATGCTTCTTTCTGACTCTA
AAATATGGAAAATAAAATATTTACAGAAACCTTTTTAAAAAAAAAAAAAAAAA

FIGURE 48

MPPPPGPAAALGTALLLLLLLASESSHTVLLRAREAAQFLRPRQRRAYQVFEEAKQGHLER
ECVEEVCSKEEAREVFENDPETEYFYPRYQECMRKYGRPEEKNPDFAKCVQNLPDQCTPN
PCDKKGTHICQDLMGNFFCVCTDGWGGRLCDKDVNECVQKNGGCSQVCHNKPGSFQCACH
SGFSLASDGQTCQDIDECTDSDTCGDARCKNLPGSYSCLCDEGYTYSSKEKTCQDVDECQ
QDRCEQTCVNSPGSYTCHCDGRGGLKLSPDMDTCEDILPCVPFSMAKSVKSLYLGRMFSG
TPVIRLRFKRLQPTRLLAEFDFRTFDPEGVLFFAGGRSDSTWIVLGLRAGRLELQLRYNG
VGRITSSGPTINHGMWQTISVEELERNLVIKVNKDAVMKIAVAGELFQLERGLYHLNLTV
GGIPFKESELVQPINPRLDGCMRSWNWLNGEDSAIQETVKANTKMQCFSVTERGSFFPGN
GFATYRLNYTRTSLDVGTETTWEVKVVARIRPATDTGVLLALVGDDDVVISVALVDYHST
KKLKKQLVVLAVEDVALALMEIKVCDSQEHTVTVSLREGEATLEVDGTKGQSEVSTAQLQ
ERLDTLKTHLQGSVHTYVGGLPEVSVISAPVTAFYRGCMTLEVNGKILDLDTASYKHSDI
TSHSCPPVEHATP

FIGURE 49

CGCCGCGCTCCCGCACCCGCGGCCCGCCCACCGCGCCGCTCCCGCATCTGCACCCGCAGC
CCGGCGGCCTCCCGGCGGGAGCGAGCAGATCCAGTCCGGCCCGCAGCGCAACTCGGTCCA
GTCGGGGCGGCGGCTGCGGGCGCAGAGCGGAGATGCAGCGGCTTGGGGCCACCCTGCTGT
GCCTGCTGCTGGCGGCGGCGGTCCCCACGGCCCCCGCGCCCGCTCCGACGGCGACCTCGG
CTCCAGTCAAGCCCGGCCCGGCTCTCAGCTACCCGCAGGAGGAGGCCACCCTCAATGAGA
TGTTCCGCGAGGTTGAGGAACTGATGGAGGACACGCAGCACAAATTGCGCAGCGCGGTGG
AAGAGATGGAGGCAGAAGAAGCTGCTGCTAAAGCATCATCAGAAGTGAACCTGGCAAACT
TACCTCCCAGCTATCACAATGAGACCAACACAGACACGAAGGTTGGAAATAATACCATCC
ATGTGCACCGAGAAATTCACAAGATAACCAACAACCAGACTGGACAAATGGTCTTTTCAG
AGACAGTTATCACATCTGTGGGAGACGAAGAAGGCAGAAGGAGCCACGAGTGCATCATCG
ACGAGGACTGTGGGCCCAGCATGTACTGCCAGTTTGCCAGCTTCCAGTACACCTGCCAGC
CATGCCGGGGCCAGAGGATGCTCTGCACCCGGGACAGTGAGTGCTGTGGAGACCAGCTGT
GTGTCTGGGGTCACTGCACCAAAATGGCCACCAGGGGCAGCAATGGGACCATCTGTGACA
ACCAGAGGGACTGCCAGCCGGGGCTGTGCTGTGCCTTCCAGAGAGGCCTGCTGTTCCCTG
TGTGCACACCCCTGCCCGTGGAGGGCGAGCTTTGCCATGACCCCGCCAGCCGGCTTCTGG
ACCTCATCACCTGGGAGCTAGAGCCTGATGGAGCCTTGGACCGATGCCCTTGTGCCAGTG
GCCTCCTCTGCCAGCCCCACAGCCACAGCCTGGTGTATGTGTGCAAGCCGACCTTCGTGG
GGAGCCGTGACCAAGATGGGGAGATCCTGCTGCCCAGAGAGGTCCCCGATGAGTATGAAG
TTGGCAGCTTCATGGAGGAGGTGCGCCAGGAGCTGGAGGACCTGGAGAGGAGCCTGACTG
AAGAGATGGCGCTGGGGGAGCCTGCGGCTGCCGCCGCTGCACTGCTGGGAGGGGAAGAGA
TTTAGATCTGGACCAGGCTGTGGGTAGATGTGCAATAGAAATAGCTAATTTATTTCCCCA
GGTGTGTGCTTTAGGCGTGGGCTGACCAGGCTTCTTCCTACATCTTCTTCCCAGTAAGTT
TCCCCTCTGGCTTGACAGCATGAGGTGTTGTGCATTTGTTCAGCTCCCCCAGGCTGTTCT
CCAGGCTTCACAGTCTGGTGCTTGGGAGAGTCAGGCAGGGTTAAACTGCAGGAGCAGTTT
GCCACCCCTGTCCAGATTATTGGCTGCTTTGCCTCTACCAGTTGGCAGACAGCCGTTTGT
TCTACATGGCTTTGATAATTGTTTGAGGGGAGGAGATGGAAACAATGTGGAGTCTCCCTC
TGATTGGTTTTGGGGAAATGTGGAGAAGAGTGCCCTGCTTTGCAAACATCAACCTGGCAA
AAATGCAACAAATGAATTTTCCACGCAGTTCTTTCCATGGGCATAGGTAAGCTGTGCCTT
CAGCTGTTGCAGATGAAATGTTCTGTTCACCCTGCATTACATGTGTTTATTCATCCAGCA
GTGTTGCTCAGCTCCTACCTCTGTGCCAGGGCAGCATTTTCATATCCAAGATCAATTCCC
TCTCTCAGCACAGCCTGGGGAGGGGGTCATTGTTCTCCTCGTCCATCAGGGATCTCAGAG
GCTCAGAGACTGCAAGCTGCTTGCCCAAGTCACACAGCTAGTGAAGACCAGAGCAGTTTC
ATCTGGTTGTGACTCTAAGCTCAGTGCTCTCTCCACTACCCCACACCAGCCTTGGTGCCA
CCAAAAGTGCTCCCCAAAAGGAAGGAGAATGGGATTTTTCTTGAGGCATGCACATCTGGA
ATTAAGGTCAAACTAATTCTCACATCCCTCTAAAAGTAAACTACTGTTAGGAACAGCAGT
GTTCTCACAGTGTGGGGCAGCCGTCCTTCTAATGAAGACAATGATATTGACACTGTCCCT
CTTTGGCAGTTGCATTAGTAACTTTGAAAGGTATATGACTGAGCGTAGCATACAGGTTAA
CCTGCAGAAACAGTACTTAGGTAATTGTAGGGCGAGGATTATAAATGAAATTTGCAAAAT
CACTTAGCAGCAACTGAAGACAATTATCAACCACGTGGAGAAAATCAAACCGAGCAGGGC
TGTGTGAAACATGGTTGTAATATGCGACTGCGAACACTGAACTCTACGCCACTCCACAAA
TGATGTTTTCAGGTGTCATGGACTGTTGCCACCATGTATTCATCCAGAGTTCTTAAAGTT
TAAAGTTGCACATGATTGTATAAGCATGCTTTCTTTGAGTTTTAAATTATGTATAAACAT
AAGTTGCATTTAGAAATCAAGCATAAATCACTTCAACTGCAAAAAAAAAAAAAAAAAAAA
AAAAAA

FIGURE 50

MQRLGATLLCLLLAAAVPTAPAPAPTATSAPVKPGPALSYPQEEATLNEMFREVEELMED
TQHKLRSAVEEMEAEEAAAKASSEVNLANLPPSYHNETNTDTKVGNNTIHVHREIHKITN
NQTGQMVFSETVITSVGDEEGRRSHECIIDEDCGPSMYCQFASFQYTCQPCRGQRMLCTR
DSECCGDQLCVWGHCTKMATRGSNGTICDNQRDCQPGLCCAFQRGLLFPVCTPLPVEGEL
CHDPASRLLDLITWELEPDGALDRCPCASGLLCQPHSHSLVYVCKPTFVGSRDQDGEILL
PREVPDEYEVGSFMEEVRQELEDLERSLTEEMALGEPAAAAAALLGGEEI

Signal sequence:
amino acids 1-19

N-glycosylation site:
amino acids 96-100, 106-110, 121-125, 204-208

Casein kinase II phosphorylation site:
amino acids 46-50, 67-71, 98-102, 135-139, 206-210, 312-316, 327-331

N-myristoylation site:
amino acids 202-208, 217-223

Amidation site:
amino acids 140-144

FIGURE 51

GCCTGTTGCTGATGCTGCCGTGCGGTACTTGTC**<u>ATG</u>**GAGCTGGCACTGCGGCGCTCTCCC
GTCCCGCGGTGGTTGCTGCTGCTGCCGCTGCTGCTGGGCCTGAACGCAGGAGCTGTCATT
GACTGGCCCACAGAGGAGGGCAAGGAAGTATGGGATTATGTGACGGTCCGCAAGGATGCC
TACATGTTCTGGTGGCTCTATTATGCCACCAACTCCTGCAAGAACTTCTCAGAACTGCCC
CTGGTCATGTGGCTTCAGGGCGGTCCAGGCGGTTCTAGCACTGGATTTGGAAACTTTGAG
GAAATTGGGCCCCTTGACAGTGATCTCAAACCACGGAAAACCACCTGGCTCCAGGCTGCC
AGTCTCCTATTTGTGGATAATCCCGTGGGCACTGGGTTCAGTTATGTGAATGGTAGTGGT
GCCTATGCCAAGGACCTGGCTATGGTGGCTTCAGACATGATGGTTCTCCTGAAGACCTTC
TTCAGTTGCCACAAAGAATTCCAGACAGTTCCATTCTACATTTTCTCAGAGTCCTATGGA
GGAAAAATGGCAGCTGGCATTGGTCTAGAGCTTTATAAGGCCATTCAGCGAGGGACCATC
AAGTGCAACTTTGCGGGGGTTGCCTTGGGTGATTCCTGGATCTCCCCTGTTGATTCGGTG
CTCTCCTGGGGACCTTACCTGTACAGCATGTCTCTTCTCGAAGACAAAGGTCTGGCAGAG
GTGTCTAAGGTTGCAGAGCAAGTACTGAATGCCGTAAATAAGGGGCTCTACAGAGAGGCC
ACAGAGCTGTGGGGGAAAGCAGAAATGATCATTGAACAGAACACAGATGGGGTGAACTTC
TATAACATCTTAACTAAAAGCACTCCCACGTCTACAATGGAGTCGAGTCTAGAATTCACA
CAGAGCCACCTAGTTTGTCTTTGTCAGCGCCACGTGAGACACCTACAACGAGATGCCTTA
AGCCAGCTCATGAATGGCCCCATCAGAAAGAAGCTCAAAATTATTCCTGAGGATCAATCC
TGGGGAGGCCAGGCTACCAACGTCTTTGTGAACATGGAGGAGGACTTCATGAAGCCAGTC
ATTAGCATTGTGGACGAGTTGCTGGAGGCAGGGATCAACGTGACGGTGTATAATGGACAG
CTGGATCTCATCGTAGATACCATGGGTCAGGAGGCCTGGGTGCGGAAACTGAAGTGGCCA
GAACTGCCTAAATTCAGTCAGCTGAAGTGGAAGGCCCTGTACAGTGACCCTAAATCTTTG
GAAACATCTGCTTTTGTCAAGTCCTACAAGAACCTTGCTTTCTACTGGATTCTGAAAGCT
GGTCATATGGTTCCTTCTGACCAAGGGGACATGGCTCTGAAGATGATGAGACTGGTGACT
CAGCAAGAA**<u>TAG</u>**GATGGATGGGGCTGGAGATGAGCTGGTTTGGCCTTGGGGCACAGAGCT
GAGCTGAGGCCGCTGAAGCTGTAGGAAGCGCCATTCTTCCCTGTATCTAACTGGGGCTGT
GATCAAGAAGGTTCTGACCAGCTTCTGCAGAGGATAAAATCATTGTCTCTGGAGGCAATT
TGGAAATTATTTCTGCTTCTTAAAAAAACCTAAGATTTTTAAAAAATTGATTTGTTTTG
ATCAAAATAAAGGATGATAATAGATATTAA

FIGURE 52

MELALRRSPVPRWLLLLPLLLGLNAGAVIDWPTEEGKEVWDYVTVRKDAYMFWWLYYATN
SCKNFSELPLVMWLQGGPGGSSTGFGNFEEIGPLDSDLKPRKTTWLQAASLLFVDNPVGT
GFSYVNGSGAYAKDLAMVASDMMVLLKTFFSCHKEFQTVPFYIFSESYGGKMAAGIGLEL
YKAIQRGTIKCNFAGVALGDSWISPVDSVLSWGPYLYSMSLLEDKGLAEVSKVAEQVLNA
VNKGLYREATELWGKAEMIIEQNTDGVNFYNILTKSTPTSTMESSLEFTQSHLVCLCQRH
VRHLQRDALSQLMNGPIRKKLKIIPEDQSWGGQATNVFVNMEEDFMKPVISIVDELLEAG
INVTVYNGQLDLIVDTMGQEAWVRKLKWPELPKFSQLKWKALYSDPKSLETSAFVKSYKN
LAFYWILKAGHMVPSDQGDMALKMMRLVTQQE

Signal sequence:
amino acids 1-25

N-glycosylation site:
amino acids 64-68, 126-130, 362-366

cAMP- and cGMP-dependent protein kinase phosphorylation site:
amino acids 101-105

Casein kinase II phosphorylation site:
amino acids 204-208, 220-224, 280-284, 284-288, 351-355, 449-453

N-myristoylation site:
amino acids 22-28, 76-82, 79-85, 80-86, 119-125, 169-175, 187-193, 195-201, 331-337, 332-338, 360-366

FIGURE 53

GTCTGTTCCCAGGAGTCCTTCGGCGGCTGTTGTGTCAGTGGCCTGATCGCGATGGGGACA
AAGGCGCAAGTCGAGAGGAAACTGTTGTGCCTCTTCATATTGGCGATCCTGTTGTGCTCC
CTGGCATTGGGCAGTGTTACAGTGCACTCTTCTGAACCTGAAGTCAGAATTCCTGAGAAT
AATCCTGTGAAGTTGTCCTGTGCCTACTCGGGCTTTTCTTCTCCCCGTGTGGAGTGGAAG
TTTGACCAAGGAGACACCACCAGACTCGTTTGCTATAATAACAAGATCACAGCTTCCTAT
GAGGACCGGGTGACCTTCTTGCCAACTGGTATCACCTTCAAGTCCGTGACACGGGAAGAC
ACTGGGACATACACTTGTATGGTCTCTGAGGAAGGCGGCAACAGCTATGGGGAGGTCAAG
GTCAAGCTCATCGTGCTTGTGCCTCCATCCAAGCCTACAGTTAACATCCCCTCCTCTGCC
ACCATTGGGAACCGGGCAGTGCTGACATGCTCAGAACAAGATGGTTCCCCACCTTCTGAA
TACACCTGGTTCAAAGATGGGATAGTGATGCCTACGAATCCCAAAAGCACCCGTGCCTTC
AGCAACTCTTCCTATGTCCTGAATCCCACAACAGGAGAGCTGGTCTTTGATCCCCTGTCA
GCCTCTGATACTGGAGAATACAGCTGTGAGGCACGGAATGGGTATGGGACACCCATGACT
TCAAATGCTGTGCGCATGGAAGCTGTGGAGCGGAATGTGGGGGTCATCGTGGCAGCCGTC
CTTGTAACCCTGATTCTCCTGGGAATCTTGGTTTTTGGCATCTGGTTTGCCTATAGCCGA
GGCCACTTTGACAGAACAAAGAAAGGGACTTCGAGTAAGAAGGTGATTTACAGCCAGCCT
AGTGCCCGAAGTGAAGGAGAATTCAAACAGACCTCGTCATTCCTGGTGTGAGCCTGGTCG
GCTCACCGCCTATCATCTGCATTTGCCTTACTCAGGTGCTACCGGACTCTGGCCCCTGAT
GTCTGTAGTTTCACAGGATGCCTTATTTGTCTTCTACACCCCACAGGGCCCCCTACTTCT
TCGGATGTGTTTTTAATAATGTCAGCTATGTGCCCCATCCTCCTTCATGCCCTCCCTCCC
TTTCCTACCACTGCTGAGTGGCCTGGAACTTGTTTAAAGTGTTTATTCCCCATTTCTTTG
AGGGATCAGGAAGGAATCCTGGGTATGCCATTGACTTCCCTTCTAAGTAGACAGCAAAAA
TGGCGGGGGTCGCAGGAATCTGCACTCAACTGCCCACCTGGCTGGCAGGGATCTTTGAAT
AGGTATCTTGAGCTTGGTTCTGGGCTCTTTCCTTGTGTACTGACGACCAGGGCCAGCTGT
TCTAGAGCGGGAATTAGAGGCTAGAGCGGCTGAAATGGTTGTTTGGTGATGACACTGGGG
TCCTTCCATCTCTGGGGCCCACTCTCTTCTGTCTTCCCATGGGAAGTGCCACTGGGATCC
CTCTGCCCTGTCCTCCTGAATACAAGCTGACTGACATTGACTGTGTCTGTGGAAAATGGG
AGCTCTTGTTGTGGAGAGCATAGTAAATTTTCAGAGAACTTGAAGCCAAAAGGATTTAAA
ACCGCTGCTCTAAAGAAAAGAAAACTGGAGGCTGGGCGCAGTGGCTCACGCCTGTAATCC
CAGAGGCTGAGGCAGGCGGATCACCTGAGGTCGGGAGTTCGGGATCAGCCTGACCAACAT
GGAGAAACCCTACTGGAAATACAAAGTTAGCCAGGCATGGTGGTGCATGCCTGTAGTCCC
AGCTGCTCAGGAGCCTGGCAACAAGAGCAAAACTCCAGCTCAAAAAAAAAAAAAAAA

FIGURE 54

MGTKAQVERKLLCLFILAILLCSLALGSVTVHSSEPEVRIPENNPVKLSCAYSGFSSPRV
EWKFDQGDTTRLVCYNNKITASYEDRVTFLPTGITFKSVTREDTGTYTCMVSEEGGNSYG
EVKVKLIVLVPPSKPTVNIPSSATIGNRAVLTCSEQDGSPPSEYTWFKDGIVMPTNPKST
RAFSNSSYVLNPTTGELVFDPLSASDTGEYSCEARNGYGTPMTSNAVRMEAVERNVGVIV
AAVLVTLILLGILVFGIWFAYSRGHFDRTKKGTSSKKVIYSQPSARSEGEFKQTSSFLV

Signal sequence:
amino acids 1-27

Transmembrane domain:
amino acids 238-255

N-glycosylation site:
amino acids 185-189

cAMP- and cGMP-dependent protein kinase phosphorylation site:
amino acids 270-274

Casein kinase II phosphorylation site:
amino acids 34-38, 82-86, 100-104, 118-122, 152-156, 154-158, 193-197, 203-207, 287-291

N-myristoylation site:
amino acids 105-111, 116-122, 158-164, 219-225, 237-243, 256-262

FIGURE 55

GTTGTGTCCTTCAGCAAAACAGTGGATTTAAATCTCCTTGCACAAGCTTGAGAGCAACAC
AATCTATCAGGAAAGAAAGAAAGAAAAAAACCGAACCTGACAAAAAAGAAGAAAAAGAAG
AAGAAAAAAAATC<u>ATG</u>AAAACCATCCAGCCAAAAATGCACAATTCTATCTCTTGGGCAAT
CTTCACGGGGCTGGCTGCTCTGTGTCTCTTCCAAGGAGTGCCCGTGCGCAGCGGAGATGC
CACCTTCCCCAAAGCTATGGACAACGTGACGGTCCGGCAGGGGGAGAGCGCCACCCTCAG
GTGCACTATTGACAACCGGGTCACCCGGGTGGCCTGGCTAAACCGCAGCACCATCCTCTA
TGCTGGGAATGACAAGTGGTGCCTGGATCCTCGCGTGGTCCTTCTGAGCAACACCCAAAC
GCAGTACAGCATCGAGATCCAGAACGTGGATGTGTATGACGAGGGCCCTTACACCTGCTC
GGTGCAGACAGACAACCACCCAAAGACCTCTAGGGTCCACCTCATTGTGCAAGTATCTCC
CAAAATTGTAGAGATTTCTTCAGATATCTCCATTAATGAAGGGAACAATATTAGCCTCAC
CTGCATAGCAACTGGTAGACCAGAGCCTACGGTTACTTGGAGACACATCTCTCCCAAAGC
GGTTGGCTTTGTGAGTGAAGACGAATACTTGGAAATTCAGGGCATCACCCGGGAGCAGTC
AGGGGACTACGAGTGCAGTGCCTCCAATGACGTGGCCGCGCCCGTGGTACGGAGAGTAAA
GGTCACCGTGAACTATCCACCATACATTTCAGAAGCCAAGGGTACAGGTGTCCCCGTGGG
ACAAAAGGGGACACTGCAGTGTGAAGCCTCAGCAGTCCCCTCAGCAGAATTCCAGTGGTA
CAAGGATGACAAAAGACTGATTGAAGGAAAGAAAGGGGTGAAAGTGGAAAACAGACCTTT
CCTCTCAAAACTCATCTTCTTCAATGTCTCTGAACATGACTATGGGAACTACACTTGCGT
GGCCTCCAACAAGCTGGGCCACACCAATGCCAGCATCATGCTATTTGGTCCAGGCGCCGT
CAGCGAGGTGAGCAACGGCACGTCGAGGAGGGCAGGCTGCGTCTGGCTGCTGCCTCTTCT
GGTCTTGCACCTGCTTCTCAAATTT<u>TGA</u>TGTGAGTGCCACTTCCCCACCCGGGAAAGGCT
GCCGCCACCACCACCACCAACACAACAGCAATGGCAACACCGACAGCAACCAATCAGATA
TATACAAATGAAATTAGAAGAAACACAGCCTCATGGGACAGAAATTTGAGGGAGGGGAAC
AAAGAATACTTTGGGGGGAAAAGAGTTTTAAAAAAGAAATTGAAAATTGCCTTGCAGATA
TTTAGGTACAATGGAGTTTTCTTTTCCCAAACGGGAAGAACACAGCACACCCGGCTTGGA
CCCACTGCAAGCTGCATCGTGCAACCTCTTTGGTGCCAGTGTGGGCAAGGGCTCAGCCTC
TCTGCCCACAGAGTGCCCCCACGTGGAACATTCTGGAGCTGGCCATCCCAAATTCAATCA
GTCCATAGAGACGAACAGAATGAGACCTTCCGGCCCAAGCGTGGCGCTGCGGGCACTTTG
GTAGACTGTGCCACCACGGCGTGTGTTGTGAAACGTGAAATAAAAAGAGCAAAAAAAAA

FIGURE 56

MKTIQPKMHNSISWAIFTGLAALCLFQGVPVRSGDATFPKAMDNVTVRQGESATLRCTID
NRVTRVAWLNRSTILYAGNDKWCLDPRVVLLSNTQTQYSIEIQNVDVYDEGPYTCSVQTD
NHPKTSRVHLIVQVSPKIVEISSDISINEGNNISLTCIATGRPEPTVTWRHISPKAVGFV
SEDEYLEIQGITREQSGDYECSASNDVAAPVVRRVKVTVNYPPYISEAKGTGVPVGQKGT
LQCEASAVPSAEFQWYKDDKRLIEGKKGVKVENRPFLSKLIFFNVSEHDYGNYTCVASNK
LGHTNASIMLFGPGAVSEVSNGTSRRAGCVWLLPLLVLHLLLKF

FIGURE 57

<u>**GCT**</u>GCGCCGGCTGCGGCTGCAGGGGAATCCGCTGTGGTGCGGCTGCCAGGCGCGGCCCCT
ACTCGAGTGGCTGGCGCGGGCGCGCGTGCGCTCGGACGGCGCGTGCCAGGGGCCGCGGCG
CCTGCGGGGCGAGGCTCTGGACGCCCTGCGGCCCTGGGACCTGCGCTGCCCTGGGGACGC
GGCGCAGGAAGAGGAAGAGCTGGAAGAGCGGGCTGTGGCCGGGCCCCGCGCCCCTCCGCG
CGGCCCTCCGCGCGGCCCCGGGGAGGAGCGGGCAGTCGCGCCTTGCCCTCGCGCCTGCGT
GTGCGTCCCCGAGTCCCGGCACAGCAGCTGCGAGGGCTGCGGCCTGCAGGCGGTGCCCCG
CGGCTTCCCCAGCGACACCCAGCTCCTGGACCTGAGGCGGAACCACTTCCCCTCGGTGCC
CCGAGCGGCCTTCCCCGGNCTGGGCCACCTGGTGTCGCTGCACCTGCAGCACTGCGGCAT
CGCGGAGCTGGAAGCGGGCGCCCTGGCCGGGCTGGGCCGCCTGATCTACCTGTACCTCTC
CGACAACCAGCTCGCAGGCCTCAGCGCTGCTGCCCTTGAAGGGGCTCCCCGCCTCGGCTA
CCTGTACCTAGAACGCAACCGTTTCCTGCAGGTGCCAGGGGCTGCCNTGCGCGCCCTGCC
CAGCCTCTTCTCCCTGCACCTGCAGGACAACGCTGTGGACCGCCTGGCACCTGGGGACCT
GGGGAGAACACGGGCCTTGCGCTGGGTCTACCTGAGTGGAAACCGCATCACCGAAGTGTC
CCTTGGGGCGCTGGGCCCAGCTCGGGAGCTGGAGAAGCTGCACCTGGACAGGAATCAGCT
GCGAGAGGTGCCCACTGGGGCCTTGGAGGGGCTGCCTGCCCTCCTGGAGCTGCAGCTCTC
GGGCAACCCACTCAGGGCCTTGCGTGACGGAGCCTTCCAGCCTGTGGGCAGGTCGCTGCA
GCACCTCTTCCTGAACAGCAGTGGCCTGGAGCAGATTTGTCCTGGGGCCTTTTCAGGCCT
GGGGCCCGGGCTCCAGAGCCTGCACCTGCAGAAGAACCAGCTTCGGGCCCTGCCTGCCCT
GCCCAGTCTCAGCCAGCTGGAGCTCATCGACCTCAGCAGCAATCCCTTCCCCTGTGACTG
CCAGCTGCTTCCGCTGCACAGGTGGCTTACTGGGCTGAACCTGCGGTGGGGGCCACCTG
CGCCACCCCTCCCAATGCCCGTGGCCAGAGGGTGAAGGCTGCAGCTGCTGTCTTTGAAGA
CTGCCCGGGCTGGGCTGCCAGAAAGGCCAAGCGGACACCAGCCTCCAGGCCCAGTGCCAG
GAGAACCCCCATCAAAGGAAGACAGTGTGGAGCAGATAAGAACATCCTCTTCCCCACATG
GTACCACACTGTGGAGCCCACCTCGCTGTCA<u>**TAG**</u>GCCTGCGGCTCTGAAGGATGGCTTTG
CCCGCTCCCGCTCTGCCCCTCAAGTGGAACCCAAGCTGGGCTCAGAATCTGTAGAGTGAG
GCCCCACCAAGGGAAACGACACCCACGGCCTGAGAGCCAGGTGGAGTCCTGCCACTCAGC
TGCCTGCCTTTGCTCCCACCCTCTCCCACCCTCAAAGAGGTCTCGAGGGGACACTCTGAA
GGCACCTGGCTCAGAACCACTGCCATCCAAGGAGCGAGGAGTCCCAGGGCTGAGCAAATG
CAGCGGGGAGGTCGGCAGTTCCCCTGCTTCCCGATCCTCATTTTCTGCTTCACTTGACTC
CTCCAGATAGGAGCTGCTCTCACTGCCCACACTGCTG

FIGURE 58

LRRLRLQGNPLWCGCQARPLLEWLARARVRSDGACQGPRRLRGEALDALRPWDLRCPGDA
AQEEEELEERAVAGPRAPPRGPPRGPGEERAVAPCPRACVCVPESRHSSCEGCGLQAVPR
GFPSDTQLLDLRRNHFPSVPRAAFPGLGHLVSLHLQHCGIAELEAGALAGLGRLIYLYLS
DNQLAGLSAAALEGAPRLGYLYLERNRFLQVPGAAXRALPSLFSLHLQDNAVDRLAPGDL
GRTRALRWVYLSGNRITEVSLGALGPARELEKLHLDRNQLREVPTGALEGLPALLELQLS
GNPLRALRDGAFQPVGRSLQHLFLNSSGLEQICPGAFSGLGPGLQSLHLQKNQLRALPAL
PSLSQLELIDLSSNPFPCDCQLLPLHRWLTGLNLRVGATCATPPNARGQRVKAAAAVFED
CPGWAARKAKRTPASRPSARRTPIKGRQCGADKNILFPTWYHTVEPTSLS

Signal sequence:
None

Transmembrane domain:
None

N-glycosylation site:
325-328

Glycosaminoglycan attachment site:
338-341

Protein kinase C phosphorylation site:
438-440

N-myristoylation site:
166-171, 186-191, 253-258, 286-291, 335-340, 339-344, 450-455

Leucine rich repeat N-terminal domain:
94-123

Leucine Rich Repeat:
125-148, 149-172, 173-196, 197-220, 221-244, 245-268, 269-292, 293-316, 318-341, 343-364, 365-386

Leucine rich repeat C-terminal domain:
374-422

FIGURE 59

CTCCCACGGTGTCCAGCGCCCAGA**ATG**CGGCTTCTGGTCCTGCTATGGGGTTGCCTGCTG
CTCCCAGGTTATGAAGCCCTGGAGGGCCCAGAGGAAATCAGCGGGTTCGAAGGGGACACT
GTGTCCCTGCAGTGCACCTACAGGGAAGAGCTGAGGGACCACCGGAAGTACTGGTGCAGG
AAGGGTGGGATCCTCTTCTCTCGCTGCTCTGGCACCATCTATGCAGAAGAAGAAGGCCAG
GAGACAATGAAGGGCAGGGTGTCCATCCGTGACAGCCGCCAGGAGCTCTCGCTCATTGTG
ACCCTGTGGAACCTCACCCTGCAAGACGCTGGGGAGTACTGGTGTGGGGTCGAAAAACGG
GGCCCCGATGAGTCTTTACTGATCTCTCTGTTCGTCTTTCCAGGACCCTGCTGTCCTCCC
TCCCCTTCTCCCACCTTCCAGCCTCTGGCTACAACACGCCTGCAGCCCAAGGCAAAAGCT
CAGCAAACCCAGCCCCCAGGATTGACTTCTCCTGGGCTCTACCCGGCAGCCACCACAGCC
AAGCAGGGGAAGACAGGGGCTGAGGCCCCTCCATTGCCAGGGACTTCCCAGTACGGGCAC
GAAAGGACTTCTCAGTACACAGGAACCTCTCCTCACCCAGCGACCTCTCCTCCTGCAGGG
AGCTCCCGCCCCCCCATGCAGCTGGACTCCACCTCAGCAGAGGACACCAGTCCAGCTCTC
AGCAGTGGCAGCTCTAAGCCCAGGGTGTCCATCCCGATGGTCCGCATACTGGCCCCAGTC
CTGGTGCTGCTGAGCCTTCTGTCAGCCGCAGGCCTGATCGCCTTCTGCAGCCACCTGCTC
CTGTGGAGAAAGGAAGCTCAACAGGCCACGGAGACACAGAGGAACGAGAAGTTCTGGCTC
TCACGCTTGACTGCGGAGGAAAAGGAAGCCCCTTCCCAGGCCCCTGAGGGGGACGTGATC
TCGATGCCTCCCCTCCACACATCTGAGGAGGAGCTGGGCTTCTCGAAGTTTGTCTCAGCG
TAGGGCAGGAGGCCCTCCTGGCCAGGCCAGCAGTGAAGCAGTATGGCTGGCTGGATCAGC
ACCGATTCCCGAAAGCTTTCCACCTCAGCCTCAGAGTCCAGCTGCCCGGACTCCAGGGCT
CTCCCCACCCTCCCCAGGCTCTCCTCTTGCATGTTCCAGCCTGACCTAGAAGCGTTTGTC
AGCCCTGGAGCCCAGAGCGGTGGCCTTGCTCTTCCGGCTGGAGACTGGGACATCCCTGAT
AGGTTCACATCCCTGGGCAGAGTACCAGGCTGCTGACCCTCAGCAGGGCCAGACAAGGCT
CAGTGGATCTGGTCTGAGTTTCAATCTGCCAGGAACTCCTGGGCCTCATGCCCAGTGTCG
GACCCTGCCTTCCTCCCACTCCAGACCCCACCTTGTCTTCCCTCCCTGGCGTCCTCAGAC
TTAGTCCCACGGTCTCCTGCATCAGCTGGTGATGAAGAGGAGCATGCTGGGGTGAGACTG
GGATTCTGGCTTCTCTTTGAACCACCTGCATCCAGCCCTTCAGGAAGCCTGTGAAAAACG
TGATTCCTGGCCCCACCAAGACCCACCAAAACCATCTCTGGGCTTGGTGCAGGACTCTGA
ATTCTAACAATGCCCAGTGACTGTCGCACTTGAGTTTGAGGGCCAGTGGGCCTGATGAAC
GCTCACACCCCTTCAGCTTAGAGTCTGCATTTGGGCTGTGACGTCTCCACCTGCCCCAAT
AGATCTGCTCTGTCTGCGACACCAGATCCACGTGGGGACTCCCCTGAGGCCTGCTAAGTC
CAGGCCTTGGTCAGGTCAGGTGCACATTGCAGGATAAGCCCAGGACCGGCACAGAAGTGG
TTGCCTTTNCCATTTGCCCTCCCTGGNCCATGCCTTCTTGCCTTTGGAAAAAATGATGAA
GAAAACCTTGGCTCCTTCCTTGTCTGGAAAGGGTTACTTGCCTATGGGTTCTGGTGGCTA
GAGAGAAAAGTAGAAAACCAGAGTGCACGTAGGTGTCTAACACAGAGGAGAGTAGGAACA
GGGCGGATACCTGAAGGTGACTCCGAGTCCAGCCCCCTGGAGAAGGGGTCGGGGGTGGTG
GTAAAGTAGCACAACTACTATTTTTTTTCTTTTTCCATTATTATTGTTTTTTAAGACAGA
ATCTCGTGCTGCTGCCCAGGCTGGAGTGCAGTGGCACGATCTGCAAACTCCGCCTCCTGG
GTTCAAGTGATTCTTCTGCCTCAGCCTCCCGAGTAGCTGGGATTACAGGCACGCACCACC
ACACCTGGCTAATTTTTGTACTTTTAGTAGAGATGGGGTTTCACCATGTTGGCCAGGCTG
GTCTTGAACTCCTGACCTCAAATGAGCCTCCTGCTTCAGTCTCCCAAATTGCCGGGATTA
CAGGCATGAGCCACTGTGTCTGGCCCTATTTCCTTTAAAAAGTGAAATTAAGAGTTGTTC
AGTATGCAAAACTTGGAAAGATGGAGGAGAAAAAGAAAAGGAAGAAAAAAAATGTCACCCA
TAGTCTCACCAGAGACTATCATTATTTCGTTTTGTTGTACTTCCTTCCACTCTTTTCTTC
TTCACATAATTTGCCGGTGTTCTTTTTACAGAGCAATTATCTTGTATATACAACTTTGTA
TCCTGCCTTTTCCACCTTATCGTTCCATCACTTTATTCCAGCACTTCTCTGTGTTTTACA
GACCTTTTTATAAATAAAATGTTCATCAGCTGCATAAAAAAAAAAAAAA

FIGURE 60

MRLLVLLWGCLLLPGYEALEGPEEISGFEGDTVSLQCTYREELRDHRKYWCRKGGILFSR
CSGTIYAEEEGQETMKGRVSIRDSRQELSLIVTLWNLTLQDAGEYWCGVEKRGPDESLLI
SLFVFPGPCCPPSPSPTFQPLATTRLQPKAKAQQTQPPGLTSPGLYPAATTAKQGKTGAE
APPLPGTSQYGHERTSQYTGTSPHPATSPPAGSSRPPMQLDSTSAEDTSPALSSGSSKPR
VSIPMVRILAPVLVLLSLLSAAGLIAFCSHLLLWRKEAQQATETQRNEKFWLSRLTAEEK
EAPSQAPEGDVISMPPLHTSEEELGFSKFVSA

Important features:
Signal peptide:
amino acids 1-17

Transmembrane domain:
amino acids 248-269

N-glycosylation site:
amino acids 96-99

Fibrinogen beta and gamma chains C-terminal domain:
amino acids 104-113

Ig like V-type domain:
amino acids 13-128

FIGURE 61

CGGGCCAGCCTGGGGCGGCCGGCCAGGAACCACCCGTTAAGGTGTCTTCTCTTTAGGGAT
GGTGAGGTTGGAAAAAGACTCCTGTAACCCTCCTCCAGGATGAACCACCTGCCAGAAGAC
ATGGAGAACGCTCTCACCGGGAGCCAGAGCTCCCATGCTTCTCTGCGCAATATCCATTCC
ATCAACCCCACACAACTCATGGCCAGGATTGAGTCCTATGAAGGAAGGGAAAAGAAAGGC
ATATCTGATGTCAGGAGGACTTTCTGTTTGTTTGTCACCTTTGACCTCTTATTCGTAACA
TTACTGTGGATAATAGAGTTAAATGTGAATGGAGGCATTGAGAACACATTAGAGAAGGAG
GTGATGCAGTATGACTACTATTCTTCATATTTTGATATATTTCTTCTGGCAGTTTTTCGA
TTTAAAGTGTTAATACTTGCATATGCTGTGTGCAGACTGCGCCATTGGTGGGCAATAGCG
TTGACAACGGCAGTGACCAGTGCCTTTTTACTAGCAAAAGTGATCCTTTCGAAGCTTTTC
TCTCAAGGGGCTTTTGGCTATGTGCTGCCCATCATTTCATTCATCCTTGCCTGGATTGAG
ACGTGGTTCCTGGATTTCAAAGTGTTACCTCAAGAAGCAGAAGAAGAAAACAGACTCCTG
ATAGTTCAGGATGCTTCAGAGAGGGCAGCACTTATACCTGGTGGTCTTTCTGATGGTCAG
TTTTATTCCCCTCCTGAATCCGAAGCAGGATCTGAAGAAGCTGAAGAAAAACAGGACAGT
GAGAAACCACTTTTAGAACTATGAGTACTACTTTTGTTAAATGTGAAAAACCCTCACAGA
AAGTCATCGAGGCAAAAAGAGGCAGGCAGTGGAGTCTCCCTGTCGACAGTAAAGTTGAAA
TGGTGACGTCCACTGCTGGCTTTATTGAACAGCTAATAAAGATTTATTTATTGTAATACC
TCACAAACGTTGTACCATATCCATGCACATTTAGTTGCCTGCCTGTGGCTGGTAAGGTAA
TGTCATGATTCATCCTCTCTTCAGTGAGACTGAGCCTGATGTGTTAACAAATAGGTGAAG
AAAGTCTTGTGCTGTATTCCTAATCAAAAGACTTAATATATTGAAGTAACACTTTTTTAG
TAAGCAAGATACCTTTTTATTTCAATTCACAGAATGGAATTTTTTTGTTTCATGTCTCAG
ATTTATTTTGTATTTCTTTTTTAACACTCTACATTTCCCTTGTTTTTTAACTCATGCACA
TGTGCTCTTTGTACAGTTTTAAAAAGTGTAATAAAATCTGACATGTCAATGTGGCTAGTT
TTATTTTTCTTGTTTTGCATTATGTGTATGGCCTGAAGTGTTGGACTTGCAAAAGGGGAA
GAAAGGAATTGCGAATACATGTAAAATGTCACCAGACATTTGTATTATTTTTATCATGAA
ATCATGTTTTTCTCTGATTGTTCTGAAATGTTCTAAATACTCTTATTTTGAATGCACAAA
ATGACTTAAACCATTCATATCATGTTTCCTTTGCGTTCAGCCAATTTCAATTAAAATGAA
CTAAATTAAAAA

FIGURE 62

MNHLPEDMENALTGSQSSHASLRNIHSINPTQLMARIESYEGREKKGISDVRRTFCLFVT
FDLLFVTLLWIIELNVNGGIENTLEKEVMQYDYYSSYFDIFLLAVFRFKVLILAYAVCRL
RHWWAIALTTAVTSAFLLAKVILSKLFSQGAFGYVLPIISFILAWIETWFLDFKVLPQEA
EEENRLLIVQDASERAALIPGGLSDGQFYSPPESEAGSEEAEEKQDSEKPLLEL

Important features of the protein:
Signal peptide:
amino acids 1-20

Transmembrane domains:
amino acids 54-72, 100-118, 130-144, 146-166

N-myristoylation sites:
amino acids 14-20, 78-84, 79-85, 202-208, 217-223

FIGURE 63

GCGCCGGGAGCCCATCTGCCCCCAGGGGCACGGGGCGCGGGGCCGGCTCCCGCCCGGCAC
ATGGCTGCAGCCACCTCGCGCGCACCCCGAGGCGCCGCGCCCAGCTCGCCCGAGGTCCGT
CGGAGGCGCCCGGCCGCCCCGGAGCCAAGCAGCAACTGAGCGGGGAAGCGCCCCGCGTCCG
GGGATCGGG<u>ATG</u>TCCCTCCTCCTTCTCCTCTTGCTAGTTTCCTACTATGTTGGAACCTTG
GGGACTCACACTGAGATCAAGAGAGTGGCAGAGGAAAAGGTCACTTTGCCCTGCCACCAT
CAACTGGGGCTTCCAGAAAAAGACACTCTGGATATTGAATGGCTGCTCACCGATAATGAA
GGGAACCAAAAAGTGGTGATCACTTACTCCAGTCGTCATGTCTACAATAACTTGACTGAG
GAACAGAAGGGCCGAGTGGCCTTTGCTTCCAATTTCCTGGCAGGAGATGCCTCCTTGCAG
ATTGAACCTCTGAAGCCCAGTGATGAGGGCCGGTACACCTGTAAGGTTAAGAATTCAGGG
CGCTACGTGTGGAGCCATGTCATCTTAAAAGTCTTAGTGAGACCATCCAAGCCCAAGTGT
GAGTTGGAAGGAGAGCTGACAGAAGGAAGTGACCTGACTTTGCAGTGTGAGTCATCCTCT
GGCACAGAGCCCATTGTGTATTACTGGCAGCGAATCCGAGAGAAAGAGGGAGAGGATGAA
CGTCTGCCTCCCAAATCTAGGATTGACTACAACCACCCTGGACGAGTTCTGCTGCAGAAT
CTTACCATGTCCTACTCTGGACTGTACCAGTGCACAGCAGGCAACGAAGCTGGGAAGGAA
AGCTGTGTGGTGCGAGTAACTGTACAGTATGTACAAAGCATCGGCATGGTTGCAGGAGCA
GTGACAGGCATAGTGGCTGGAGCCCTGCTGATTTTCCTCTTGGTGTGGCTGCTAATCCGA
AGGAAAGACAAAGAAAGATATGAGGAAGAAGAGAGACCTAATGAAATTCGAGAAGATGCT
GAAGCTCCAAAAGCCCGTCTTGTGAAACCCAGCTCCTCTTCCTCAGGCTCTCGGAGCTCA
CGCTCTGGTTCTTCCTCCACTCGCTCCACAGCAAATAGTGCCTCACGCAGCCAGCGGACA
CTGTCAACTGACGCAGCACCCCAGCCAGGGCTGGCCACCCAGGCATACAGCCTAGTGGGG
CCAGAGGTGAGAGGTTCTGAACCAAAGAAAGTCCACCATGCTAATCTGACCAAAGCAGAA
ACCACACCCAGCATGATCCCCAGCCAGAGCAGAGCCTTCCAAACGGTC<u>TGA</u>ATTACAATG
GACTTGACTCCCACGCTTTCCTAGGAGTCAGGGTCTTTGGACTCTTCTCGTCATTGGAGC
TCAAGTCACCAGCCACACAACCAGATGAGAGGTCATCTAAGTAGCAGTGAGCATTGCACG
GAACAGATTCAGATGAGCATTTTCCTTATACAATACCAAACAAGCAAAAGGATGTAAGCT
GATTCATCTGTAAAAAGGCATCTTATTGTGCCTTTAGACCAGAGTAAGGGAAAGCAGGAG
TCCAAATCTATTTGTTGACCAGGACCTGTGGTGAGAAGGTTGGGGAAAGGTGAGGTGAAT
ATACCTAAAACTTTTAATGTGGGATATTTTGTATCAGTGCTTTGATTCACAATTTTCAAG
AGGAAATGGGATGCTGTTTGTAAATTTTCTATGCATTTCTGCAAACTTATTGGATTATTA
GTTATTCAGACAGTCAAGCAGAACCCACAGCCTTATTACACCTGTCTACACCATGTACTG
AGCTAACCACTTCTAAGAAACTCCAAAAAAGGAAACATGTGTCTTCTATTCTGACTTAAC
TTCATTTGTCATAAGGTTTGGATATTAATTTCAAGGGGAGTTGAAATAGTGGGAGATGGA
GAAGAGTGAATGAGTTTCTCCCACTCTATACTAATCTCACTATTTGTATTGAGCCCAAAA
TAACTATGAAAGGAGACAAAAATTTGTGACAAAGGATTGTGAAGAGCTTTCCATCTTCAT
GATGTTATGAGGATTGTTGACAAACATTAGAAATATATAATGGAGCAATTGTGGATTTCC
CCTCAAATCAGATGCCTCTAAGGACTTTCCTGCTAGATATTTCTGGAAGGAGAAAATACA
ACATGTCATTTATCAACGTCCTTAGAAAGAATTCTTCTAGAGAAAAAGGATCTAGGAAT
GCTGAAAGATTACCCAACATACCATTATAGTCTCTTCTTTCTGAGAAAATGTGAAACCAG
AATTGCAAGACTGGGTGGACTAGAAAGGGAGATTAGATCAGTTTTCTCTTAATATGTCAA
GGAAGGTAGCCGGGCATGGTGCCAGGCACCTGTAGGAAAATCCAGCAGGTGGAGGTTGCA
GTGAGCCGAGATTATGCCATTGCACTCCAGCCTGGGTGACAGAGCGGGACTCCGTCTC

FIGURE 64

MSLLLLLLLVSYYVGTLGTHTEIKRVAEEKVTLPCHHQLGLPEKDTLDIEWLLTDNEGNQ
KVVITYSSRHVYNNLTEEQKGRVAFASNFLAGDASLQIEPLKPSDEGRYTCKVKNSGRYV
WSHVILKVLVRPSKPKCELEGELTEGSDLTLQCESSSGTEPIVYYWQRIREKEGEDERLP
PKSRIDYNHPGRVLLQNLTMSYSGLYQCTAGNEAGKESCVVRVTVQYVQSIGMVAGAVTG
IVAGALLIFLLVWLLIRRKDKERYEEEERPNEIREDAEAPKARLVKPSSSSSGSRSSRSG
SSSTRSTANSASRSQRTLSTDAAPQPGLATQAYSLVGPEVRGSEPKKVHHANLTKAETTP
SMIPSQSRAFQTV

Signal sequence:
amino acids 1-16

Transmembrane domain:
amino acids 232-251

FIGURE 65

GTCGGGGCTGCGCGACGGCGCAGGGGCTGCGGGGAGCGCCGCGCAGGCCGTGCAGTTCCT
AGCGAGGAGGCGCCGCCGCCATTGCCGCTCTCTCGGTGAGCGCAGCCCCGCTCTCCGGGC
CGGGCCTTCGCGGGCCACCGGCGCC**<u>ATG</u>**GGCCAGTGCGGCATCACCTCCTCCAAGACCGT
GCTGGTCTTTCTCAACCTCATCTTCTGGGGGGCAGCTGGCATTTTATGCTATGTGGGAGC
CTATGTCTTCATCACTTATGATGACTATGACCACTTCTTTGAAGATGTGTACACGCTCAT
CCCTGCTGTAGTGATCATAGCTGTAGGAGCCCTGCTTTTCATCATTGGGCTAATTGGCTG
CTGTGCCACAATCCGGGAAAGTCGCTGTGGACTTGCCACGTTTGTCATCATCCTGCTCTT
GGTTTTTGTCACAGAAGTTGTTGTAGTGGTTTTGGGATATGTTTACAGAGCAAAGGTGGA
AAATGAGGTTGATCGCAGCATTCAGAAAGTGTATAAGACCTACAATGGAACCAACCCTGA
TGCTGCTAGCCGGGCTATTGATTATGTACAGAGACAGCTGCATTGTTGTGGAATTCACAA
CTACTCAGACTGGGAAAATACAGATTGGTTCAAAGAAACCAAAAACCAGAGTGTCCCTCT
TAGCTGCTGCAGAGAGACTGCCAGCAATTGTAATGGCAGCCTGGCCCACCCTTCCGACCT
CTATGCTGAGGGGTGTGAGGCTCTAGTAGTGAAGAAGCTACAAGAAATCATGATGCATGT
GATCTGGGCCGCACTGGCATTTGCAGCTATTCAGCTGCTGGGCATGCTGTGTGCTTGCAT
CGTGTTGTGCAGAAGGAGTAGAGATCCTGCTTACGAGCTCCTCATCACTGGCGGAACCTA
TGCA**<u>TAG</u>**TTGACAACTCAAGCCTGAGCTTTTTGGTCTTGTTCTGATTTGGAAGGTGAATT
GAGCAGGTCTGCTGCTGTTGGCCTCTGGAGTTCATTTAGTTAAAGCACATGTACACTGGT
GTTGGACAGAGCAGCTTGGCTTTTCATGTGCCCACCTACTTACCTACTACCTGCGACTTT
CTTTTTCCTTGTTCTAGCTGACTCTTCATGCCCCTAAGATTTTAAGTACGATGGTGAACG
TTCTAATTTCAGAACCAATTGCGAGTCATGTAGTGTGGTAGAATTAAAGGAGGACACGAG
CCTGCTTCTGTTACCTCCAAGTGGTAACAGGACTGATGCCGAAATGTCACCAGGTCCTTT
CAGTCTTCACAGTGGAGAACTCTTGGCCAAAGGTTTTTGCGGGGAGGAGGAGGAAACCAG
CTTTCTGGTTAAGGTTAACACCAGATGGTGCCCCTCATTGGTGTCCTTTTAAAAAATATT
TACTGTAGTCCAATAAGATAGCAGCTGTACAAAATGACTAAAATAGATTGTAGGATCATA
TGGCGTATATCTTGGTTCATCTTCAAAATCAGAGACTGAGCTTTGAAACTAGTGGTTTTT
AATCAAAGTTGGCTTTATAGGAGGAGTATAATGTATGCACTACTGTTTTAAAAGAATTAG
TGTGAGTGTGTTTTTGTATGAATGAGCCCATTCATGGTAAGTCTTAAGCTTGTTGGAAAT
AATGTACCCATGTAGACTAGCAAAATAGTATGTAGATGTGATCTCAGTTGTAAATAGAAA
AATCTAATTCAATAAACTCTGTATCAGCCCCCAAAAAAAAAAAAAAAA

FIGURE 66

MGQCGITSSKTVLVFLNLIFWGAAGILCYVGAYVFITYDDYDHFFEDVYTLIPAVVIIAV
GALLFIIGLIGCCATIRESRCGLATFVIILLLVFVTEVVVVVLGYVYRAKVENEVDRSIQ
KVYKTYNGTNPDAASRAIDYVQRQLHCCGIHNYSDWENTDWFKETKNQSVPLSCCRETAS
NCNGSLAHPSDLYAEGCEALVVKKLQEIMMHVIWAALAFAAIQLLGMLCACIVLCRRSRD
PAYELLITGGTYA

Signal peptide:
none

Type II transmembrane domain:
11-38

Other transmembrane domains:
48-68, 87-107, 208-235

N-glycosylation site:
127-131, 152-156, 167-171, 183-187

Tyrosine kinase phosphorylation site:
236-244

N-myristoylation site:
5-11, 68-74, 71-77, 226-232

Prokaryotic membrane lipoprotein lipid attachment site:
62-73, 221-232

Transmembrane 4 family proteins:
7-35, 56-106

FIGURE 67

GCGGCACCTGGAAG**ATG**CGCCCATTGGCTGGTGGCCTGCTCAAGGTGGTGTTCGTGGTCT
TCGCCTCCTTGTGTGCCTGGTATTCGGGGTACCTGCTCGCAGAGCTCATTCCAGATGCAC
CCCTGTCCAGTGCTGCCTATAGCATCCGCAGCATCGGGGAGAGGCCTGTCCTCAAAGCTC
CAGTCCCCAAAAGGCAAAAATGTGACCACTGGACTCCCTGCCCATCTGACACCTATGCCT
ACAGGTTACTCAGCGGAGGTGGCAGAAGCAAGTACGCCAAAATCTGCTTTGAGGATAACC
TACTTATGGGAGAACAGCTGGGAAATGTTGCCAGAGGAATAAACATTGCCATTGTCAACT
ATGTAACTGGGAATGTGACAGCAACACGATGTTTTGATATGTATGAAGGCGATAACTCTG
GACCGATGACAAAGTTTATTCAGAGTGCTGCTCCAAAATCCCTGCTCTTCATGGTGACCT
ATGACGACGGAAGCACAAGACTGAATAACGATGCCAAGAATGCCATAGAAGCACTTGGAA
GTAAAGAAATCAGGAACATGAAATTCAGGTCTAGCTGGGTATTTATTGCAGCAAAAGGCT
TGGAACTCCCTTCCGAAATTCAGAGAGAAAAGATCAACCACTCTGATGCTAAGAACAACA
GATATTCTGGCTGGCCTGCAGAGATCCAGATAGAAGGCTGCATACCCAAAGAACGAAGC**T**
GACACTGCAGGGTCCTGAGTAAATGTGTTCTGTATAAACAAATGCAGCTGGAATCGCTCA
AGAATCTTATTTTTCTAAATCCAACAGCCCATATTTGATGAGTATTTTGGGTTTGTTGTA
AACCAATGAACATTTGCTAGTTGTATCAAATCTTGGTACGCAGTATTTTTATACCAGTAT
TTTATGTAGTGAAGATGTCAATTAGCAGGAAACTAAAATGAATGGAAATTCTTAAAAAAA
AAA

FIGURE 68

MRPLAGGLLKVVFVVFASLCAWYSGYLLAELIPDAPLSSAAYSIRSIGERPVLKAPVPKR
QKCDHWTPCPSDTYAYRLLSGGGRSKYAKICFEDNLLMGEQLGNVARGINIAIVNYVTGN
VTATRCFDMYEGDNSGPMTKFIQSAAPKSLLFMVTYDDGSTRLNNDAKNAIEALGSKEIR
NMKFRSSWVFIAAKGLELPSEIQREKINHSDAKNNRYSGWPAEIQIEGCIPKERS

Signal sequence:
amino acids 1-20

N-glycosylation sites:
amino acids 120-124, 208-212

Glycosaminoglycan attachment site:
amino acids 80-84

N-myristoylation sites:
amino acids 81-87, 108-114, 119-125

FIGURE 69

ACACAACTTTACACCTGAATGAACGCCAAACCTCTATGGATATATAAAGGGAAGCTTGAG
GAGGAATTTCACAGTTACAGTGCAGAAGCAGAAGCAAAAGAATTAACCAGCTCTTCAGTC
AAGCAAATCCTCTACTCACC<u>ATG</u>CTTCCTCCTGCCATTCATTTCTATCTCCTTCCCCTTG
CATGCATCCTAATGAAAAGCTGTTTGGCTTTTAAAAATGATGCCACAGAAATCCTTTATT
CACATGTGGTTAAACCTGTTCCAGCACACCCCAGCAGCAACAGCACGTTGAATCAAGCCA
GAAATGGAGGCAGGCATTTCAGTAACACTGGACTGGATCGGAACACTCGGGTTCAAGTGG
GTTGCCGGGAACTGCGTTCCACCAAATACATCTCTGATGGCCAGTGCACCAGCATCAGCC
CTCTGAAGGAGCTGGTGTGTGCTGGCGAGTGCTTGCCCCTGCCAGTGCTCCCTAACTGGA
TTGGAGGAGGCTATGGAACAAAGTACTGGAGCAGGAGGAGCTCCCAGGAGTGGCGGTGTG
TCAATGACAAAACCCGTACCCAGAGAATCCAGCTGCAGTGCCAAGATGGCAGCACACGCA
CCTACAAAATCACAGTAGTCACTGCCTGCAAGTGCAAGAGGTACACCCGGCAGCACAACG
AGTCCAGTCACAACTTTGAGAGCATGTCACCTGCCAAGCCAGTCCAGCATCACAGAGAGC
GGAAAAGAGCCAGCAAATCCAGCAAGCACAGCATGAGT<u>TAG</u>AACTCAGACTCCCATAACT
AGACTTACTAGTAACCATCTGCTTTACAGATTTGATTGCTTGGAAGACTCAAGCCTGCCA
CTGCTGTTTTCTCACTTGAAAGTATATGCTTTCTGCTTTGATCAAACCCAGCAAGCTGTC
TTAAGTATCAGGACCTTCTTTGGGAATAGTTTTTCCTTTTAAAGTTTTTCAAGATGTAGG
TATATCCATGAATGCAATTTGCATTTAAATTCCACGTATCCCTGTAGTTTAAATTCCTCA
TTGGTCTTAAAAGACTGTTGATACTATAAACATCAGTGGAATCAATTATATTTTAAAACA
GAAAAGGGCTT

FIGURE 70

MLPPAIHFYLLPLACILMKSCLAFKNDATEILYSHVVKPVPAHPSSNSTLNQARNGGRHF
SNTGLDRNTRVQVGCRELRSTKYISDGQCTSISPLKELVCAGECLPLPVLPNWIGGGYGT
KYWSRRSSQEWRCVNDKTRTQRIQLQCQDGSTRTYKITVVTACKCKRYTRQHNESSHNFE
SMSPAKPVQHHRERKRASKSSKHSMS

Signal sequence:
1-23

Transmembrane domain:
None

N-glycosylation site:
47-50, 173-176

cAMP- and cGMP-dependent protein kinase phosphorylation site:
125-128, 166-169, 195-198

N-myristoylation site:
64-69, 87-92, 115-120, 116-121, 150-155

FIGURE 71

CCCAGGCTCTAGTGCAGGAGGAGAAGGAGGAGGAGCAGGAGGTGGAGATTCCCAGTTAAA
AGGCTCCAGAATCGTGTACCAGGCAGAGAACTGAAGTACTGGGGCCTCCTCCACTGGGTC
CGAATCAGTAGGTGACCCCGCCCCTGGATTCTGGAAGACCTCACC<u>ATG</u>GGACGCCCCCGA
CCTCGTGCGGCCAAGACGTGGATGTTCCTGCTCTTGCTGGGGGGAGCCTGGGCAGGACAC
TCCAGGGCACAGGAGGACAAGGTGCTGGGGGGTCATGAGTGCCAACCCCATTCGCAGCCT
TGGCAGGCGGCCTTGTTCCAGGGCCAGCAACTACTCTGTGGCGGTGTCCTTGTAGGTGGC
AACTGGGTCCTTACAGCTGCCCACTGTAAAAAACCGAAATACACAGTACGCCTGGGAGAC
CACAGCCTACAGAATAAAGATGGCCCAGAGCAAGAAATACCTGTGGTTCAGTCCATCCCA
CACCCCTGCTACAACAGCAGCGATGTGGAGGACCACAACCATGATCTGATGCTTCTTCAA
CTGCGTGACCAGGCATCCCTGGGGTCCAAAGTGAAGCCCATCAGCCTGGCAGATCATTGC
ACCCAGCCTGGCCAGAAGTGCACCGTCTCAGGCTGGGGCACTGTCACCAGTCCCCGAGAG
AATTTTCCTGACACTCTCAACTGTGCAGAAGTAAAAATCTTTCCCCAGAAGAAGTGTGAG
GATGCTTACCCGGGGCAGATCACAGATGGCATGGTCTGTGCAGGCAGCAGCAAAGGGGCT
GACACGTGCCAGGGCGATTCTGGAGGCCCCCTGGTGTGTGATGGTGCACTCCAGGGCATC
ACATCCTGGGGCTCAGACCCCTGTGGGAGGTCCGACAAACCTGGCGTCTATACCAACATC
TGCCGCTACCTGGACTGGATCAAGAAGATCATAGGCAGCAAGGGC<u>TGA</u>TTCTAGGATAAG
CACTAGATCTCCCTTAATAAACTCACAACTCTCTGGTTC

FIGURE 72

MGRPRPRAAKTWMFLLLLGGAWAGHSRAQEDKVLGGHECQPHSQPWQAALFQGQQLLCGG
VLVGGNWVLTAAHCKKPKYTVRLGDHSLQNKDGPEQEIPVVQSIPHPCYNSSDVEDHNHD
LMLLQLRDQASLGSKVKPISLADHCTQPGQKCTVSGWGTVTSPRENFPDTLNCAEVKIFP
QKKCEDAYPGQITDGMVCAGSSKGADTCQGDSGGPLVCDGALQGITSWGSDPCGRSDKPG
VYTNICRYLDWIKKIIGSKG

Important Features:
Signal peptide:
amino acids 1-23

Transmembrane domain:
amino acids 51-71

N-glycosylation site:
amino acids 110-113

Serine proteases, trypsin family, histidine active site:
amino acids 69-74 and 207-217

Tyrosine kinase phosphorylation site:
amino acids 182-188

Kringle domain proteins motif:
amino acids 205-217

FIGURE 73

CTCGGGCGCGCACAGGCAGCTCGGTTTGCCCTGCGATTGAGCTGCGGGTCGCGGCCGGCG
CCGGCCTCTCCAATGGCAAATGTGTGTGGCTGGAGGCGAGCGCGAGGCTTTCGGCAAAGG
CAGTCGAGTGTTTGCAGACCGGGGCGAGTCCTGTGAAAGCAGATAAAAGAAAACATTTAT
TAACGTGTCATTACGAGGGGAGCGCCCGGCCGGGGCTGTCGCACTCCCCGCGGAACATTT
GGCTCCCTCCAGCTCCGAGAGAGGAGAAGAAGAAAGCGGAAAAGAGGCAGATTCACGTCG
TTTCCAGCCAAGTGGACCTGATCGATGGCCCTCCTGAATTTATCACGATATTTGATTTAT
TAGCGATGCCCCCTGGTTTGTGTGTTACGCACACACACGTGCACACAAGGCTCTGGCTCG
CTTCCCTCCCTCGTTTCCAGCTCCTGGGCGAATCCCACATCTGTTTCAACTCTCCGCCGA
GGGCGAGCAGGAGCGAGAGTGTGTCGAATCTGCGAGTGAAGAGGGACGAGGGAAAAGAAA
CAAAGCCACAGACGCAACTTGAGACTCCCGCATCCCAAAAGAAGCACCAGATCAGCAAAA
AAAGAAG<u>ATG</u>GGCCCCCCGAGCCTCGTGCTGTGCTTGCTGTCCGCAACTGTGTTCTCCCT
GCTGGGTGGAAGCTCGGCCTTCCTGTCGCACCACCGCCTGAAAGGCAGGTTTCAGAGGGA
CCGCAGGAACATCCGCCCCAACATCATCCTGGTGCTGACGGACGACCAGGATGTGGAGCT
GGGTTCCATGCAGGTGATGAACAAGACCCGGCGCATCATGGAGCAGGGCGGGGCGCACTT
CATCAACGCCTTCGTGACCACACCCATGTGCTGCCCCTCACGCTCCTCCATCCTCACTGG
CAAGTACGTCCACAACCACAACACCTACACCAACAATGAGAACTGCTCCTCGCCCTCCTG
GCAGGCACAGCACGAGAGCCGCACCTTTGCCGTGTACCTCAATAGCACTGGCTACCGGAC
AGCTTTCTTCGGGAAGTATCTTAATGAATACAACGGCTCCTACGTGCCACCCGGCTGGAA
GGAGTGGGTCGGACTCCTTAAAAACTCCCGCTTTTATAACTACACGCTGTGTCGGAACGG
GGTGAAAGAGAAGCACGGCTCCGACTACTCCAAGGATTACCTCACAGACCTCATCACCAA
TGACAGCGTGAGCTTCTTCCGCACGTCCAAGAAGATGTACCCGCACAGGCCAGTCCTCAT
GGTCATCAGCCATGCAGCCCCCCACGGCCCTGAGGATTCAGCCCCACAATATTCACGCCT
CTTCCCAAACGCATCTCAGCACATCACGCCGAGCTACAACTACGCGCCCAACCCGGACAA
ACACTGGATCATGCGCTACACGGGGCCCATGAAGCCCATCCACATGGAATTCACCAACAT
GCTCCAGCGGAAGCGCTTGCAGACCCTCATGTCGGTGGACGACTCCATGGAGACGATTTA
CAACATGCTGGTTGAGACGGGCGAGCTGGACAACACGTACATCGTATACACCGCCGACCA
CGGTTACCACATCGGCCAGTTTGGCCTGGTGAAAGGGAAATCCATGCCATATGAGTTTGA
CATCAGGGTCCCGTTCTACGTGAGGGGCCCCAACGTGGAAGCCGGCTGTCTGAATCCCCA
CATCGTCCTCAACATTGACCTGGCCCCCACCATCCTGGACATTGCAGGCCTGGACATACC
TGCGGATATGGACGGGAAATCCATCCTCAAGCTGCTGGACACGGAGCGGCCGGTGAATCG
GTTTCACTTGAAAAAGAAGATGAGGGTCTGGCGGGACTCCTTCTTGGTGGAGAGAGGCAA
GCTGCTACACAAGAGAGACAATGACAAGGTGGACGCCCAGGAGGAGAACTTTCTGCCCAA
GTACCAGCGTGTGAAGGACCTGTGTCAGCGTGCTGAGTACCAGACGGCGTGTGAGCAGCT
GGGACAGAAGTGGCAGTGTGTGGAGGACGCCACGGGGAAGCTGAAGCTGCATAAGTGCAA
GGGCCCCATGCGGCTGGGCGGCAGCAGAGCCCTCTCCAACCTCGTGCCCAAGTACTACGG
GCAGGGCAGCGAGGCCTGCACCTGTGACAGCGGGGACTACAAGCTCAGCCTGGCCGGACG
CCGGAAAAAACTCTTCAAGAAGAAGTACAAGGCCAGCTATGTCCGCAGTCGCTCCATCCG
CTCAGTGGCCATCGAGGTGGACGGCAGGGTGTACCACGTAGGCCTGGGTGATGCCGCCCA
GCCCCGAAACCTCACCAAGCGGCACTGGCCAGGGGCCCCTGAGGACCAAGATGACAAGGA
TGGTGGGGACTTCAGTGGCACTGGAGGCCTTCCCGACTACTCAGCCGCCAACCCCATTAA
AGTGACACATCGGTGCTACATCCTAGAGAACGACACAGTCCAGTGTGACCTGGACCTGTA
CAAGTCCCTGCAGGCCTGGAAAGACCACAAGCTGCACATCGACCACGAGATTGAAACCCT
GCAGAACAAAATTAAGAACCTGAGGGAAGTCCGAGGTCACCTGAAGAAAAAGCGGCCAGA
AGAATGTGACTGTCACAAAATCAGCTACCACACCCAGCACAAAGGCCGCCTCAAGCACAG
AGGCTCCAGTCTGCATCCTTTCAGGAAGGGCCTGCAAGAGAAGGACAAGGTGTGGCTGTT
GCGGGAGCAGAAGCGCAAGAAGAAACTCCGCAAGCTGCTCAAGCGCCTGCAGAACAACGA
CACGTGCAGCATGCCAGGCCTCACGTGCTTCACCCACGACAACCAGCACTGGCAGACGGC

GCCTTTCTGGACACTGGGGCCTTTCTGTGCCTGCACCAGCGCCAACAATAACACGTACTG
GTGCATGAGGACCATCAATGAGACTCACAATTTCCTCTTCTGTGAATTTGCAACTGGCTT
CCTAGAGTACTTTGATCTCAACACAGACCCCTACCAGCTGATGAATGCAGTGAACACACT
GGACAGGGATGTCCTCAACCAGCTACACGTACAGCTCATGGAGCTGAGGAGCTGCAAGGG
TTACAAGCAGTGTAACCCCCGGACTCGAAACATGGACCTGGATGGAGGAAGCTATGAGCA
ATACAGGCAGTTTCAGCGTCGAAAGTGGCCAGAAATGAAGAGACCTTCTTCCAAATCACT
GGGACAACTGTGGGAAGGCTGGGAAGGT**<u>TAA</u>**GAAACAACAGAGGTGGACCTCCAAAAACA
TAGAGGCATCACCTGACTGCACAGGCAATGAAAAACCATGTGGGTGATTTCCAGCAGACC
TGTGCTATTGGCCAGGAGGCCTGAGAAAGCAAGCACGCACTCTCAGTCAACATGACAGAT
TCTGGAGGATAACCAGCAGGAGCAGAGATAACTTCAGGAAGTCCATTTTTGCCCCTGCTT
TTGCTTTGGATTATACCTCACCAGCTGCACAAAATGCATTTTTTCGTATCAAAAAGTCAC
CACTAACCCTCCCCCAGAAGCTCACAAAGGAAAACGGAGAGAGCGAGCGAGAGAGATTTC
CTTGGAAATTTCTCCCAAGGGCGAAAGTCATTGGAATTTTTAAATCATAGGGGAAAAGCA
GTCCTGTTCTAAATCCTCTTATTCTTTTGGTTTGTCACAAAGAAGGAACTAAGAAGCAGG
ACAGAGGCAACGTGGAGAGGCTGAAAACAGTGCAGAGACGTTTGACAATGAGTCAGTAGC
ACAAAAGAGATGACATTTACCTAGCACTATAAACCCTGGTTGCCTCTGAAGAAACTGCCT
TCATTGTATATATGTGACTATTTACATGTAATCAACATGGGAACTTTTAGGGGAACCTAA
TAAGAAATCCCAATTTTCAGGAGTGGTGGTGTCAATAAACGCTCTGTGGCCAGTGTAAAA
GAAAAA

FIGURE 74

MGPPSLVLCLLSATVFSLLGGSSAFLSHHRLKGRFQRDRRNIRPNIILVLTDDQDVELGS
MQVMNKTRRIMEQGGAHFINAFVTTPMCCPSRSSILTGKYVHNHNTYTNNENCSSPSWQA
QHESRTFAVYLNSTGYRTAFFGKYLNEYNGSYVPPGWKEWVGLLKNSRFYNYTLCRNGVK
EKHGSDYSKDYLTDLITNDSVSFFRTSKKMYPHRPVLMVISHAAPHGPEDSAPQYSRLFP
NASQHITPSYNYAPNPDKHWIMRYTGPMKPIHMEFTNMLQRKRLQTLMSVDDSMETIYNM
LVETGELDNTYIVYTADHGYHIGQFGLVKGKSMPYEFDIRVPFYVRGPNVEAGCLNPHIV
LNIDLAPTILDIAGLDIPADMDGKSILKLLDTERPVNRFHLKKKMRVWRDSFLVERGKLL
HKRDNDKVDAQEENFLPKYQRVKDLCQRAEYQTACEQLGQKWQCVEDATGKLKLHKCKGP
MRLGGSRALSNLVPKYYGQGSEACTCDSGDYKLSLAGRRKKLFKKKYKASYVRSRSIRSV
AIEVDGRVYHVGLGDAAQPRNLTKRHWPGAPEDQDDKDGGDFSGTGGLPDYSAANPIKVT
HRCYILENDTVQCDLDLYKSLQAWKDHKLHIDHEIETLQNKIKNLREVRGHLKKKRPEEC
DCHKISYHTQHKGRLKHRGSSLHPFRKGLQEKDKVWLLREQKRKKKLRKLLKRLQNNDTC
SMPGLTCFTHDNQHWQTAPFWTLGPFCACTSANNNTYWCMRTINETHNFLFCEFATGFLE
YFDLNTDPYQLMNAVNTLDRDVLNQLHVQLMELRSCKGYKQCNPRTRNMDLDGGSYEQYR
QFQRRKWPEMKRPSSKSLGQLWEGWEG

Important features:
Signal peptide:
amino acids 1-17

Sulfatases signature 1:
amino acids 86-99

Homologous region to sulfatase:
amino acids 87-106, 133-146, 216-229, 291-320, 365-375

N-glycosylation sites:
amino acids 65-69, 112-116, 132-136, 149-153, 171-175, 198-202, 241-245, 561-565, 608-612, 717-721, 754-758, 764-768

FIGURE 75

CCCACGCGTCCGCCCACGCGTCCGGTGGACTATGGGCCAGTTTTTGTGCAAGAACCAGAT
GATATTATTTTTCCAACTGATTCTGATGAAAAGAAGGTAGCATTGAATTGTGAAGTTCGT
GGCAATCCAGTTCCCAGTTACAGATGGCTTCGAAATGGAACAGAAATAGATCTGGAAAGT
GATTATCGCTACAGTTTGATAGATGGCACCTTCATTATAAGCAATCCAAGTGAAGCAAAG
GATTCTGGTCATTATCAGTGTTTAGCAACCAACACTGTGGGGAGTATTCTTAGTAGAGAA
GCTACACTGCAGTTTGCCTATCTGGGAAATTTTAGTGGCCGGACAAGAAGTGCAGTCTCT
GTGAGGGAAGGCCAGGGTGTCGTTCTG**ATG**TGCTCTCCTCCGCCACATTCACCAGAGATC
ATCTATAGCTGGGTATTTAATGAGTTCCCTTCCTTTGTGGCGGAAGACAGCCGGCGGTTC
ATCTCCCAGGAGACAGGCAACCTTTATATTTCTAAAGTCCAAACATCAGATGTTGGCAGC
TATATTTGTCTGGTGAAAAACACAGTGACGAATGCTAGAGTCCTTAGTCCTCCAACGCCA
CTCACTCTGCGTAATGATGGTGTGATGGGAGAATATGAGCCGAAAATTGAGGTCCATTTT
CCTTTCACGGTTACAGCTGCTAAAGGAACAACTGTTAAGATGGAATGCTTTGCACTTGGC
AACCCCGTTCCAACAATCACATGGATGAAGGTTAATGGTTATATTCCTAGTAAGGCACGT
CTGCGGAAATCTCAGGCGGTGCTGGAAATACCGAATGTACAGCTGGATGATGCAGGCATT
TATGAGTGCAGAGCTGAAAACTCACGTGGAAAAAATTCCTTTCGTGGACAATTACAAGTA
TACACCTACCCACACTGGGTAGAAAAACTGAATGATACTCAGTTAGACAGTGGGAGCCCT
CTCCGATGGGAATGTAAGGCTACTGGAAAACCCAGACCCACGTATCGTTGGCTGAAGAAT
GGAGTACCCCTCTCACCTCAGAGTAGGGTTGAGATGGTTAATGGAGTATTGATGATCCAC
AATGTGAATCAATCAGATGCTGGAATGTATCAGTGTTTGGCTGAAAATAAGTATGGAGCC
ATTTACGCTAGTGCTGAGCTGAAGATTCTAGCTTCAGCTCCCACTTTTGCACTGAATCAA
CTGAAGAAAACAATAATTGTTACCAAAGACCAAGAAGTTGTCATAGAGTGCAAACCCCAA
GGCTCTCCAAAACCAACCATCTCTTGGAAGAAAGGAGACAGAGCAGTTAGAGAAAACAAA
AGAATAGCTATTCTTCCAGACGGGAGTCTACGGATCCTAAATGCTTCCAAATCAGACGAG
GGAAAGTACGTTTGCCGAGGGGAAAACGTCTTTGGTTCTGCTGAAAT

FIGURE 76

MCSPPPHSPEIIYSWVFNEFPSFVAEDSRRFISQETGNLYISKVQTSDVGSYICLVKNTV
TNARVLSPPTPLTLRNDGVMGEYEPKIEVHFPFTVTAAKGTTVKMECFALGNPVPTITWM
KVNGYIPSKARLRKSQAVLEIPNVQLDDAGIYECRAENSRGKNSFRGQLQVYTYPHWVEK
LNDTQLDSGSPLRWECKATGKPRPTYRWLKNGVPLSPQSRVEMVNGVLMIHNVNQSDAGM
YQCLAENKYGAIYASAELKILASAPTFALNQLKKTIIVTKDQEVVIECKPQGSPKPTISW
KKGDRAVRENKRIAILPDGSLRILNASKSDEGKYVCRGENVFGSAE

Signal sequence:
None

Transmembrane domain:
None

N-glycosylation site:
182-185, 234-237, 325-328

Tyrosine kinase phosphorylation site:
328-334

N-myristoylation site:
50-55, 150-155, 239-244, 250-255

Immunoglobulin domain:
2-56, 100-156, 189-245, 281-338

FIGURE 77

GCTCCCAGCCAAGAACCTCGGGGCCGCTGCGCGGTGGGGAGGAGTTCCCCGAAACCCGGC
CGCTAAGCGAGGCCTCCTCCTCCCGCAGATCCGAACGGCCTGGGCGGGGTCACCCCGGCT
GGGACAAGAAGCCGCCGCCTGCCTGCCCGGGCCCGGGGAGGGGGCTGGGGCTGGGGCCGG
AGGCGGGGTGTGAGTGGGTGTGTGCGGGGGGCGGAGGCTTGATGCAATCCCGATAAGAAA
TGCTCGGGTGTCTTGGGCACCTACCCGTGGGGCCCGTAAGGCGCTACTATATAAGGCTGC
CGGCCCGGAGCCGCCGCGCCGTCAGAGCAGGAGCGCTGCGTCCAGGATCTAGGGCCACGA
CCATCCCAACCCGGCACTCACAGCCCCGCAGCGCATCCCGGTCGCCGCCCAGCCTCCCGC
ACCCCCATCGCCGGAGCTGCGCCGAGAGCCCCAGGGAGGTGCC**ATG**CGGAGCGGGTGTGT
GGTGGTCCACGTATGGATCCTGGCCGGCCTCTGGCTGGCCGTGGCCGGGCGCCCCCTCGC
CTTCTCGGACGCGGGGCCCCACGTGCACTACGGCTGGGGCGACCCCATCCGCCTGCGGCA
CCTGTACACCTCCGGCCCCCACGGGCTCTCCAGCTGCTTCCTGCGCATCCGTGCCGACGG
CGTCGTGGACTGCGCGCGGGGCCAGAGCGCGCACAGTTTGCTGGAGATCAAGGCAGTCGC
TCTGCGGACCGTGGCCATCAAGGGCGTGCACAGCGTGCGGTACCTCTGCATGGGCGCCGA
CGGCAAGATGCAGGGGCTGCTTCAGTACTCGGAGGAAGACTGTGCTTTCGAGGAGGAGAT
CCGCCCAGATGGCTACAATGTGTACCGATCCGAGAAGCACCGCCTCCCGGTCTCCCTGAG
CAGTGCCAAACAGCGGCAGCTGTACAAGAACAGAGGCTTTCTTCCACTCTCTCATTTCCT
GCCCATGCTGCCCATGGTCCCAGAGGAGCCTGAGGACCTCAGGGGCCACTTGGAATCTGA
CATGTTCTCTTCGCCCCTGGAGACCGACAGCATGGACCCATTTGGGCTTGTCACCGGACT
GGAGGCCGTGAGGAGTCCCAGCTTTGAGAAG**TAA**CTGAGACCATGCCCGGGCCTCTTCAC
TGCTGCCAGGGGCTGTGGTACCTGCAGCGTGGGGGACGTGCTTCTACAAGAACAGTCCTG
AGTCCACGTTCTGTTTAGCTTTAGGAAGAAACATCTAGAAGTTGTACATATTCAGAGTTT
TCCATTGGCAGTGCCAGTTTCTAGCCAATAGACTTGTCTGATCATAACATTGTAAGCCTG
TAGCTTGCCCAGCTGCTGCCTGGGCCCCCATTCTGCTCCCTCGAGGTTGCTGGACAAGCT
GCTGCACTGTCTCAGTTCTGCTTGAATACCTCCATCGATGGGGAACTCACTTCCTTTGGA
AAAATTCTTATGTCAAGCTGAAATTCTCTAATTTTTTCTCATCACTTCCCCAGGAGCAGC
CAGAAGACAGGCAGTAGTTTTAATTTCAGGAACAGGTGATCCACTCTGTAAAACAGCAGG
TAAATTTCACTCAACCCCATGTGGGAATTGATCTATATCTCTACTTCCAGGGACCATTTG
CCCTTCCCAAATCCCTCCAGGCCAGAACTGACTGGAGCAGGCATGGCCCACCAGGCTTCA
GGAGTAGGGGAAGCCTGGAGCCCCACTCCAGCCCTGGGACAACTTGAGAATTCCCCCTGA
GGCCAGTTCTGTCATGGATGCTGTCCTGAGAATAACTTGCTGTCCCGGTGTCACCTGCTT
CCATCTCCCAGCCCACCAGCCCTCTGCCCACCTCACATGCCTCCCCATGGATTGGGGCCT
CCCAGGCCCCCCACCTTATGTCAACCTGCACTTCTTGTTCAAAAATCAGGAAAAGAAAAG
ATTTGAAGACCCCAAGTCTTGTCAATAACTTGCTGTGTGGAAGCAGCGGGGGAAGACCTA
GAACCCTTTCCCCAGCACTTGGTTTTCCAACATGATATTTATGAGTAATTTATTTTGATA
TGTACATCTCTTATTTTCTTACATTATTTATGCCCCCAAATTATATTTATGTATGTAAGT
GAGGTTTGTTTTGTATATTAAAATGGAGTTTGTTTGT

FIGURE 78

MRSGCVVVHVWILAGLWLAVAGRPLAFSDAGPHVHYGWGDPIRLRHLYTSGPHGLSSCFL
RIRADGVVDCARGQSAHSLLEIKAVALRTVAIKGVHSVRYLCMGADGKMQGLLQYSEEDC
AFEEEIRPDGYNVYRSEKHRLPVSLSSAKQRQLYKNRGFLPLSHFLPMLPMVPEEPEDLR
GHLESDMFSSPLETDSMDPFGLVTGLEAVRSPSFEK

Signal peptide:
amino acids 1-22

Casein kinase II phosphorylation site:
amino acids 78-82, 116-120, 190-194, 204-208

N-myristoylation site:
amino acids 15-21, 54-60, 66-72, 201-207

Prokaryotic membrane lipoprotein lipid attachment site:
amino acids 48-59

FIGURE 79

CGGACGCGTGGGCGGACGCGTGGGCCTGGGCAAGGGCCGGGGCGCCGGGCCGAGCCACCTCTTCCC
CTCCCCCGCTTCCCTGTCGCGCTCCGCTGGCTGGACGCGCTGGAGGAGTGGAGCAGCACCCGGCCG
GCCCTGGGGGCTGACAGTCGGCAAAGTTTGGCCCGAAGAGGAAGTGGTCTCAAACCCCGGCAGGTG
GCGACCAGGCCAGACCAGGGGCGCTCGCTGCCTGCGGGCGGGCTGTAGGCGAGGGCGCGCCCCAGT
GCCGAGACCCGGGGCTTCAGGAGCCGGCCCCGGGAGAGAAGAGTGCGGCGGCGGACGGAGAAAACA
ACTCCAAAGTTGGCGAAAGGCACCGCCCCTACTCCCGGGCTGCCGCCGCCTCCCCGCCCCCAGCCC
TGGCATCCAGAGTACGGGTCGAGCCCGGGCCATGGAGCCCCCCTGGGGAGGCGGCACCAGGGAGCC
TGGGCGCCCGGGGCTCCGCCGCGACCCCATCGGGTAGACCACAGAAGCTCCGGGACCCTTCCGGCA
CCTCTGGACAGCCCAGG**ATG**CTGTTGGCCACCCTCCTCCTCCTCCTCCTTGGAGGCGCTCTGGCCC
ATCCAGACCGGATTATTTTTCCAAATCATGCTTGTGAGGACCCCCCAGCAGTGCTCTTAGAAGTGC
AGGGCACCTTACAGAGGCCCCTGGTCCGGGACAGCCGCACCTCCCCTGCCAACTGCACCTGGCTCA
TCCTGGGCAGCAAGGAACAGACTGTCACCATCAGGTTCCAGAAGCTACACCTGGCCTGTGGCTCAG
AGCGCTTAACCCTACGCTCCCCTCTCCAGCCACTGATCTCCCTGTGTGAGGCACCTCCCAGCCCTC
TGCAGCTGCCCGGGGGCAACGTCACCATCACTTACAGCTATGCTGGGGCCAGAGCACCCATGGGCC
AGGGCTTCCTGCTCTCCTACAGCCAAGATTGGCTGATGTGCCTGCAGGAAGAGTTTCAGTGCCTGA
ACCACCGCTGTGTATCTGCTGTCCAGCGCTGTGATGGGGTTGATGCCTGTGGCGATGGCTCTGATG
AAGCAGGTTGCAGCTCAGACCCCTTCCCTGGCCTGACCCCAAGACCCGTCCCCTCCCTGCCTTGCA
ATGTCACCTTGGAGGACTTCTATGGGGTCTTCTCCTCTCCTGGATATACACACCTAGCCTCAGTCT
CCCACCCCCAGTCCTGCCATTGGCTGCTGGACCCCCATGATGGCCGGCGGCTGGCCGTGCGCTTCA
CAGCCCTGGACTTGGGCTTTGGAGATGCAGTGCATGTGTATGACGGCCCTGGGCCCCCTGAGAGCT
CCCGACTACTGCGTAGTCTCACCCACTTCAGCAATGGCAAGGCTGTCACTGTGGAGACACTGTCTG
GCCAGGCTGTTGTGTCCTACCACACAGTTGCTTGGAGCAATGGTCGTGGCTTCAATGCCACCTACC
ATGTGCGGGGCTATTGCTTGCCTTGGGACAGACCCTGTGGCTTAGGCTCTGGCCTGGGAGCTGGCG
AAGGCCTAGGTGAGCGCTGCTACAGTGAGGCACAGCGCTGTGACGGCTCATGGGACTGTGCTGACG
GCACAGATGAGGAGGACTGCCCAGGCTGCCCACCTGGACACTTCCCCTGTGGGGCTGCTGGCACCT
CTGGTGCCACAGCCTGCTACCTGCCTGCTGACCGCTGCAACTACCAGACTTTCTGTGCTGATGGAG
CAGATGAGAGACGCTGTCGGCATTGCCAGCCTGGCAATTTCCGATGCCGGGACGAGAAGTGCGTGT
ATGAGACGTGGGTGTGCGATGGGCAGCCAGACTGTGCGGACGGCAGTGATGAGTGGGACTGCTCCT
ATGTTCTGCCCCGCAAGGTCATTACAGCTGCAGTCATTGGCAGCCTAGTGTGCGGCCTGCTCCTGG
TCATCGCCCTGGGCTGCACCTGCAAGCTCTATGCCATTCGCACCCAGGAGTACAGCATCTTTGCCC
CCCTCTCCCGGATGGAGGCTGAGATTGTGCAGCAGCAGGCACCCCCTTCCTACGGGCAGCTCATTG
CCCAGGGTGCCATCCCACCTGTAGAAGACTTTCCTACAGAGAATCCTAATGATAACTCAGTGCTGG
GCAACCTGCGTTCTCTGCTACAGATCTTACGCCAGGATATGACTCCAGGAGGTGGCCCAGGTGCCC
GCCGTCGTCAGCGGGGCCGCTTGATGCGACGCCTGGTACGCCGTCTCCGCCGCTGGGGCTTGCTCC
CTCGAACCAACACCCCGGCTCGGGCCTCTGAGGCCAGATCCCAGGTCACACCTTCTGCTGCTCCCC
TTGAGGCCCTAGATGGTGGCACAGGTCCAGCCCGTGAGGGCGGGGCAGTGGGTGGCAAGATGGGG
AGCAGGCACCCCCACTGCCCATCAAGGCTCCCCTCCCATCTGCTAGCACGTCTCCAGCCCCCACTA
CTGTCCCTGAAGCCCCAGGGCCACTGCCCTCACTGCCCCTAGAGCCATCACTATTGTCTGGAGTGG
TGCAGGCCCTGCGAGGCCGCCTGTTGCCCAGCCTGGGGCCCCCAGGACCAACCCGGAGCCCCCCTG
GACCCCACACAGCAGTCCTGGCCCTGGAAGATGAGGACGATGTGCTACTGGTGCCACTGGCTGAGC
CGGGGGTGTGGGTAGCTGAGGCAGAGGATGAGCCACTGCTTACC**TGA**GGGGACCTGGGGGCTCTAC
TGAGGCCTCTCCCCTGGGGGCTCTACTCATAGTGGCACAACCTTTTAGAGGTGGGTCAGCCTCCCC
TCCACCACTTCCTTCCCTGTCCCTGGATTTCAGGGACTTGGTGGGCCTCCCGTTGACCCTATGTAG
CTGCTATAAAGTTAAGTGTCCCTCAGGCAGGGAGAGGGCTCACAGAGTCTCCTCTGTACGTGGCCA
TGGCCAGACACCCCAGTCCCTTCACCACCACCTGCTCCCCACGCCACCACCATTTGGGTGGCTGTT
TTTAAAAAGTAAAGTTCTTAGAGGATCATAGGTCTGGACACTCCATCCTTGCCAAACCTCTACCCA
AAAGTGGCCTTAAGCACCGGAATGCCAATTAACTAGAGACCCTCCAGCCCCCAAGGGGAGGATTTG
GGCAGAACCTGAGGTTTTGCCATCCACAATCCCTCCTACAGGGCCTGGCTCACAAAAAGAGTGCAA
CAAATGCTTCTATTCCATAGCTACGGCATTGCTCAGTAAGTTGAGGTCAAAAATAAAGGAATCATA
CATCTC

FIGURE 80

MLLATLLLLLLGGALAHPDRIIFPNHACEDPPAVLLEVQGTLQRPLVRDSRTSPANCTWL
ILGSKEQTVTIRFQKLHLACGSERLTLRSPLQPLISLCEAPPSPLQLPGGNVTITYSYAG
ARAPMGQGFLLSYSQDWLMCLQEEFQCLNHRCVSAVQRCDGVDACGDGSDEAGCSSDPFP
GLTPRPVPSLPCNVTLEDFYGVFSSPGYTHLASVSHPQSCHWLLDPHDGRRLAVRFTALD
LGFGDAVHVYDGPGPPESSRLLRSLTHFSNGKAVTVETLSGQAVVSYHTVAWSNGRGFNA
TYHVRGYCLPWDRPCGLGSGLGAGEGLGERCYSEAQRCDGSWDCADGTDEEDCPGCPPGH
FPCGAAGTSGATACYLPADRCNYQTFCADGADERRCRHCQPGNFRCRDEKCVYETWVCDG
QPDCADGSDEWDCSYVLPRKVITAAVIGSLVCGLLLVIALGCTCKLYAIRTQEYSIFAPL
SRMEAEIVQQQAPPSYGQLIAQGAIPPVEDFPTENPNDNSVLGNLRSLLQILRQDMTPGG
GPGARRRQRGRLMRRLVRRLRRWGLLPRTNTPARASEARSQVTPSAAPLEALDGGTGPAR
EGGAVGGQDGEQAPPLPIKAPLPSASTSPAPTTVPEAPGPLPSLPLEPSLLSGVVQALRG
RLLPSLGPPGPTRSPPGPHTAVLALEDEDDVLLVPLAEPGVWVAEAEDEPLLT

Important features:
Signal peptide:
amino acids 1-16

Transmembrane domain:
amino acids 442-462

LDL-receptor class A (LDLRA) domain proteins:
amino acids 411-431, 152-171, 331-350 and 374-393

FIGURE 81

CTTCTGTGCTGTTCCTTCTTGCCTCTAACTTGTAAACAAGACGTACTAGGACGATGCTAA
TGGAAAGTCACAAACCGCTGGGTTTTTGAAAGGATCCTTGGGACCTCATGCACATTTGTG
GAAACTGGATGGAGAGATTTGGGGAAGC<u>ATG</u>GACTCTTTAGCCAGCTTAGTTCTCTGTGG
AGTCAGCTTGCTCCTTTCTGGAACTGTGGAAGGTGCCATGGACTTGATCTTGATCAATTC
CCTACCTCTTGTATCTGATGCTGAAACATCTCTCACCTGCATTGCCTCTGGGTGGCGCCC
CCATGAGCCCATCACCATAGGAAGGGACTTTGAAGCCTTAATGAACCAGCACCAGGATCC
GCTGGAAGTTACTCAAGATGTGACCAGAGAATGGGCTAAAAAAGTTGTTTGGAAGAGAGA
AAAGGCTAGTAAGATCAATGGTGCTTATTTCTGTGAAGGGCGAGTTCGAGGAGAGGCAAT
CAGGATACGAACCATGAAGATGCGTCAACAAGCTTCCTTCCTACCAGCTACTTTAACTAT
GACTGTGGACAAGGGAGATAACGTGAACATATCTTTCAAAAAGGTATTGATTAAAGAAGA
AGATGCAGTGATTTACAAAAATGGTTCCTTCATCCATTCAGTGCCCCGGCATGAAGTACC
TGATATTCTAGAAGTACACCTGCCTCATGCTCAGCCCCAGGATGCTGGAGTGTACTCGGC
CAGGTATATAGGAGGAAACCTCTTCACCTCGGCCTTCACCAGGCTGATAGTCCGGAGATG
TGAAGCCCAGAAGTGGGGACCTGAATGCAACCATCTCTGTACTGCTTGTATGAACAATGG
TGTCTGCCATGAAGATACTGGAGAATGCATTTGCCCTCCTGGGTTTATGGGAAGGACGTG
TGAGAAGGCTTGTGAACTGCACACGTTTGGCAGAACTTGTAAAGAAAGGTGCAGTGGACA
AGAGGGATGCAAGTCTTATGTGTTCTGTCTCCCTGACCCCTATGGGTGTTCCTGTGCCAC
AGGCTGGAAGGGTCTGCAGTGCAATGAAGCATGCCACCCTGGTTTTTACGGGCCAGATTG
TAAGCTTAGGTGCAGCTGCAACAATGGGGAGATGTGTGATCGCTTCCAAGGATGTCTCTG
CTCTCCAGGATGGCAGGGGCTCCAGTGTGAGAGAGAAGGCATACCGAGGATGACCCCAAA
GATAGTGGATTTGCCAGATCATATAGAAGTAAACAGTGGTAAATTTAATCCCATTTGCAA
AGCTTCTGGCTGGCCGCTACCTACTAATGAAGAAATGACCCTGGTGAAGCCGGATGGGAC
AGTGCTCCATCCAAAAGACTTTAACCATACGGATCATTTCTCAGTAGCCATATTCACCAT
CCACCGGATCCTCCCCCCTGACTCAGGAGTTTGGGTCTGCAGTGTGAACACAGTGGCTGG
GATGGTGGAAAAGCCCTTCAACATTTCTGTTAAAGTTCTTCCAAAGCCCCTGAATGCCCC
AAACGTGATTGACACTGGACATAACTTTGCTGTCATCAACATCAGCTCTGAGCCTTACTT
TGGGGATGGACCAATCAAATCCAAGAAGCTTCTATACAAACCCGTTAATCACTATGAGGC
TTGGCAACATATTCAAGTGACAAATGAGATTGTTACACTCAACTATTTGGAACCTCGGAC
AGAATATGAACTCTGTGTGCAACTGGTCCGTCGTGGAGAGGGTGGGGAAGGGCATCCTGG
ACCTGTGAGACGCTTCACAACAGCTTCTATCGGACTCCCTCCTCCAAGAGGTCTAAATCT
CCTGCCTAAAAGTCAGACCACTCTAAATTTGACCTGGCAACCAATATTTCCAAGCTCGGA
AGATGACTTTTATGTTGAAGTGGAGAGAAGGTCTGTGCAAAAAAGTGATCAGCAGAATAT
TAAAGTTCCAGGCAACTTGACTTCGGTGCTACTTAACAACTTACATCCCAGGGAGCAGTA
CGTGGTCCGAGCTAGAGTCAACACCAAGGCCCAGGGGGAATGGAGTGAAGATCTCACTGC
TTGGACCCTTAGTGACATTCTTCCTCCTCAACCAGAAAACATCAAGATTTCCAACATTAC
ACACTCCTCGGCTGTGATTTCTTGGACAATATTGGATGGCTATTCTATTTCTTCTATTAC
TATCCGTTACAAGGTTCAAGGCAAGAATGAAGACCAGCACGTTGATGTGAAGATAAAGAA
TGCCACCATCATTCAGTATCAGCTCAAGGGCCTAGAGCCTGAAACAGCATACCAGGTGGA
CATTTTTGCAGAGAACAACATAGGGTCAAGCAACCCAGCCTTTTCTCATGAACTGGTGAC
CCTCCCAGAATCTCAAGCACCAGCGGACCTCGGAGGGGGGAAGATGCTGCTTATAGCCAT
CCTTGGCTCTGCTGGAATGACCTGCCTGACTGTGCTGTTGGCCTTTCTGATCATATTGCA
ATTGAAGAGGGCAAATGTGCAAAGGAGAATGGCCCAAGCCTTCCAAAACGTGAGGGAAGA
ACCAGCTGTGCAGTTCAACTCAGGGACTCTGGCCCTAAACAGGAAGGTCAAAAACAACCC
AGATCCTACAATTTATCCAGTGCTTGACTGGAATGACATCAAATTTCAAGATGTGATTGG
GGAGGGCAATTTTGGCCAAGTTCTTAAGGCGCGCATCAAGAAGGATGGGTTACGGATGGA
TGCTGCCATCAAAAGAATGAAAGAATATGCCTCCAAAGATGATCACAGGGACTTTGCAGG
AGAACTGGAAGTTCTTTGTAAACTTGGACACCATCCAAACATCATCAATCTCTTAGGAGC

ATGTGAACATCGAGGCTACTTGTACCTGGCCATTGAGTACGCGCCCCATGGAAACCTTCT
GGACTTCCTTCGCAAGAGCCGTGTGCTGGAGACGGACCCAGCATTTGCCATTGCCAATAG
CACCGCGTCCACACTGTCCTCCCAGCAGCTCCTTCACTTCGCTGCCGACGTGGCCCGGGG
CATGGACTACTTGAGCCAAAAACAGTTTATCCACAGGGATCTGGCTGCCAGAAACATTTT
AGTTGGTGAAAACTATGTGGCAAAAATAGCAGATTTTGGATTGTCCCGAGGTCAAGAGGT
GTACGTGAAAAAGACAATGGGAAGGCTCCCAGTGCGCTGGATGGCCATCGAGTCACTGAA
TTACAGTGTGTACACAACCAACAGTGATGTATGGTCCTATGGTGTGTTACTATGGGAGAT
TGTTAGCTTAGGAGGCACACCCTACTGCGGGATGACTTGTGCAGAACTCTACGAGAAGCT
GCCCCAGGGCTACAGACTGGAGAAGCCCCTGAACTGTGATGATGAGGTGTATGATCTAAT
GAGACAATGCTGGCGGGAGAAGCCTTATGAGAGGCCATCATTTGCCCAGATATTGGTGTC
CTTAAACAGAATGTTAGAGGAGCGAAAGACCTACGTGAATACCACGCTTTATGAGAAGTT
TACTTATGCAGGAATTGACTGTTCTGCTGAAGAAGCGGCC<u>TAG</u>GACAGAACATCTGTATA
CCCTCTGTTTCCCTTTCACTGGCATGGGAGACCCTTGACAACTGCTGAGAAAACATGCCT
CTGCCAAAGGATGTGATATATAAGTGTACATATGTGCTGGAATTCTAACAAGTCATAGGT
TAATATTTAAGACACTGAAAAATCTAAGTGATATAAATCAGATTCTTCTCTCTCATTTTA
TCCCTCACCTGTAGCATGCCAGTCCCGTTTCATTTAGTCATGTGACCACTCTGTCTTGTG
TTTCCACAGCCTGCAAGTTCAGTCCAGGATGCTAACATCTAAAAATAGACTTAAATCTCA
TTGCTTACAAGCCTAAGAATCTTTAGAGAAGTATACATAAGTTTAGGATAAAATAATGGG
ATTTTCTTTTCTTTTCTCTGGTAATATTGACTTGTATATTTTAAGAAATAACAGAAAGCC
TGGGTGACATTTGGGAGACATGTGACATTTATATATTGAATTAATATCCCTACATGTATT
GCACATTGTAAAAAGTTTTAGTTTTGATGAGTTGTGAGTTTACCTTGTATACTGTAGGCA
CACTTTGCACTGATATATCATGAGTGAATAAATGTCTTGCCTACTCAAAAAAAAAAAA

FIGURE 82

MDSLASLVLCGVSLLLSGTVEGAMDLILINSLPLVSDAETSLTCIASGWRPHEPITIGRD
FEALMNQHQDPLEVTQDVTREWAKKVVWKREKASKINGAYFCEGRVRGEAIRIRTMKMRQ
QASFLPATLTMTVDKGDNVNISFKKVLIKEEDAVIYKNGSFIHSVPRHEVPDILEVHLPH
AQPQDAGVYSARYIGGNLFTSAFTRLIVRRCEAQKWGPECNHLCTACMNNGVCHEDTGEC
ICPPGFMGRTCEKACELHTFGRTCKERCSGQEGCKSYVFCLPDPYGCSCATGWKGLQCNE
ACHPGFYGPDCKLRCSCNNGEMCDRFQGCLCSPGWQGLQCEREGIPRMTPKIVDLPDHIE
VNSGKFNPICKASGWPLPTNEEMTLVKPDGTVLHPKDFNHTDHFSVAIFTIHRILPPDSG
VWVCSVNTVAGMVEKPFNISVKVLPKPLNAPNVIDTGHNFAVINISSEPYFGDGPIKSKK
LLYKPVNHYEAWQHIQVTNEIVTLNYLEPRTEYELCVQLVRRGEGGEGHPGPVRRFTTAS
IGLPPPRGLNLLPKSQTTLNLTWQPIFPSSEDDFYVEVERRSVQKSDQQNIKVPGNLTSV
LLNNLHPREQYVVRARVNTKAQGEWSEDLTAWTLSDILPPQPENIKISNITHSSAVISWT
ILDGYSISSITIRYKVQGKNEDQHVDVKIKNATIIQYQLKGLEPETAYQVDIFAENNIGS
SNPAFSHELVTLPESQAPADLGGGKMLLIAILGSAGMTCLTVLLAFLIILQLKRANVQRR
MAQAFQNVREEPAVQFNSGTLALNRKVKNNPDPTIYPVLDWNDIKFQDVIGEGNFGQVLK
ARIKKDGLRMDAAIKRMKEYASKDDHRDFAGELEVLCKLGHHPNIINLLGACEHRGYLYL
AIEYAPHGNLLDFLRKSRVLETDPAFAIANSTASTLSSQQLLHFAADVARGMDYLSQKQF
IHRDLAARNILVGENYVAKIADFGLSRGQEVYVKKTMGRLPVRWMAIESLNYSVYTTNSD
VWSYGVLLWEIVSLGGTPYCGMTCAELYEKLPQGYRLEKPLNCDDEVYDLMRQCWREKPY
ERPSFAQILVSLNRMLEERKTYVNTTLYEKFTYAGIDCSAEEAA

Signal sequence:
1-38

Transmembrane domain:
750-770

N-glycosylation site:
140-143, 158-161, 399-402, 438-441, 464-467, 560-563, 596-599, 649-652, 691-694, 930-933, 1011-1014, 1104-1107

cAMP- and cGMP-dependent protein kinase phosphorylation site:
534-537

Tyrosine kinase phosphorylation site:
149-156, 808-816, 1094-1102

N-myristoylation site:
18-23, 98-103, 187-192, 196-201, 270-275, 286-291, 295-300, 420-425, 595-600, 984-989, 1036-1041, 1041-1046, 1115-1120

Prokaryotic membrane lipoprotein lipid attachment site:
882-892

EGF-like domain cysteine pattern signature:
240-251, 287-298, 329-340

Tyrosine protein kinases specific active-site signature:
960-972

Protein kinase domain:
824-1092

Fibronectin type III domain:
444-529, 543-626, 639-724

EGF-like domain:
220-251, 268-298

laminin_EGF Laminin EGF-like (Domains III and V):
219-268

Immunoglobulin domain:
156-193

Zinc finger:
295-313

Receptor tyrosine kinase:
844-868, 869-898, 936-982, 986-1024, 1025-1052, 1052-1088

FIGURE 83

CGCGCCGGGCGCAGGGAGCTGAGTGGACGGCTCGAGACGGCGGCGCGTGCAGCAGCTCCA
GAAAGCAGCGAGTTGGCAGAGCAGGGCTGCATTTCCAGCAGGAGCTGCGAGCACAGTGCT
GGCTCACAACAAG**ATG**CTCAAGGTGTCAGCCGTACTGTGTGTGTGTGCAGCCGCTTGGTG
CAGTCAGTCTCTCGCAGCTGCCGCGGCGGTGGCTGCAGCCGGGGGGCGGTCGGACGGCGG
TAATTTTCTGGATGATAAACAATGGCTCACCACAATCTCTCAGTATGACAAGGAAGTCGG
ACAGTGGAACAAATTCCGAGACGAAGTAGAGGATGATTATTTCCGCACTTGGAGTCCAGG
AAAACCCTTCGATCAGGCTTTAGATCCAGCTAAGGATCCATGCTTAAAGATGAAATGTAG
TCGCCATAAAGTATGCATTGCTCAAGATTCTCAGACTGCAGTCTGCATTAGTCACCGGAG
GCTTACACACAGGATGAAAGAAGCAGGAGTAGACCATAGGCAGTGGAGGGGTCCCATATT
ATCCACCTGCAAGCAGTGCCCAGTGGTCTATCCCAGCCCTGTTTGTGGTTCAGATGGTCA
TACCTACTCTTTTCAGTGCAAACTAGAATATCAGGCATGTGTCTTAGGAAAACAGATCTC
AGTCAAATGTGAAGGACATTGCCCATGTCCTTCAGATAAGCCCACCAGTACAAGCAGAAA
TGTTAAGAGAGCATGCAGTGACCTGGAGTTCAGGGAAGTGGCAAACAGATTGCGGGACTG
GTTCAAGGCCCTTCATGAAAGTGGAAGTCAAAACAAGAAGACAAAAACATTGCTGAGGCC
TGAGAGAAGCAGATTCGATACCAGCATCTTGCCAATTTGCAAGGACTCACTTGGCTGGAT
GTTTAACAGACTTGATACAAACTATGACCTGCTATTGGACCAGTCAGAGCTCAGAAGCAT
TTACCTTGATAAGAATGAACAGTGTACCAAGGCATTCTTCAATTCTTGTGACACATACAA
GGACAGTTTAATATCTAATAATGAGTGGTGCTACTGCTTCCAGAGACAGCAAGACCCACC
TTGCCAGACTGAGCTCAGCAATATTCAGAAGCGGCAAGGGGTAAAGAAGCTCCTAGGACA
GTATATCCCCCTGTGTGATGAAGATGGTTACTACAAGCCAACACAATGTCATGGCAGTGT
TGGACAGTGCTGGTGTGTTGACAGATATGGAAATGAAGTCATGGGATCCAGAATAAATGG
TGTTGCAGATTGTGCTATAGATTTTGAGATCTCCGGAGATTTTGCTAGTGGCGATTTTCA
TGAATGGACTGATGATGAGGATGATGAAGACGATATTATGAATGATGAAGATGAAATTGA
AGATGATGATGAAGATGAAGGGGATGATGATGATGGTGGTGATGACCATGATGTATACAT
T**TGA**TTGATGACAGTTGAAATCAATAAATTCTACATTTCTAATATTTACAAAAATGATAG
CCTATTTAAAATTATCTTCTTCCCCAATAACAAAATGATTCTAAACCTCACATATATTTT
GTATAATTATTTGAAAAATTGCAGCTAAAGTTATAGAACTTTATGTTTAAATAAGAATCA
TTTGCTTTGAGTTTTTATATTCCTTACACAAAAAGAAAATACATATGCAGTCTAGTCAGA
CAAAATAAAGTTTTGAAGTGCTACTATAATAAATTTTTCACGAGAACAAACTTTGTAAAT
CTTCCATAAGCAAAATGACAGCTAGTGCTTGGGATCGTACATGTTAATTTTTTGAAAGAT
AATTCTAAGTGAAATTTAAAATAAATAAATTTTTAATGACCTGGGTCTTAAGGATTTAGG
AAAAATATGCATGCTTTAATTGCATTTCCAAAGTAGCATCTTGCTAGACCTAGATGAGTC
AGGATAACAGAGAGATACCACATGACTCCAAAAAAAAAAAAAAA

FIGURE 84

MLKVSAVLCVCAAAWCSQSLAAAAAVAAAGGRSDGGNFLDDKQWLTTISQYDKEVGQWNK
FRDEVEDDYFRTWSPGKPFDQALDPAKDPCLKMKCSRHKVCIAQDSQTAVCISHRRLTHR
MKEAGVDHRQWRGPILSTCKQCPVVYPSPVCGSDGHTYSFQCKLEYQACVLGKQISVKCE
GHCPCPSDKPTSTSRNVKRACSDLEFREVANRLRDWFKALHESGSQNKKTKTLLRPERSR
FDTSILPICKDSLGWMFNRLDTNYDLLLDQSELRSIYLDKNEQCTKAFFNSCDTYKDSLI
SNNEWCYCFQRQQDPPCQTELSNIQKRQGVKKLLGQYIPLCDEDGYYKPTQCHGSVGQCW
CVDRYGNEVMGSRINGVADCAIDFEISGDFASGDFHEWTDDEDDEDDIMNDEDEIEDDDE
DEGDDDDGGDDHDVYI

Important features:
Signal peptide:
amino acids 1-16

Leucine zipper pattern:
amino acids 246-267

N-myristoylation sites:
amino acids 357-362, 371-376 and 376-381

Thyroglobulin type-1 repeat proteins:
amino acids 353-365 and 339-352

FIGURE 85

CCCACGCGTCCGGCACTGCAGTCTCCAGCCTGAGCC<u>ATG</u>GGCCGCCGAGCCCTCCTGCTC
CTGCTTCTGTCTTTTCTGGCGCCCTGGGCCACCATAGCCCTCCGGCCGGCCTTAAGGGCC
CTCGGCAGCCTACACTTGCCAACCAACCCCACATCCCTCCCGGCTGTAGCCAAGAACTAT
TCGGTTCTCTACTTCCAACAGAAGGTTGATCATTTTGGATTTAATACTGTGAAAACTTTT
AATCAGCGGTACCTAGTAGCTGATAAATACTGGAAGAAAAATGGTGGATCAATACTTTTC
TACACTGGTAATGAAGGGGACATTATCTGGTTTTGTAATAACACGGGGTTCATGTGGGAT
GTGGCTGAGGAACTGAAAGCTATGTTGGTGTTTGCTGAACATCGATACTATGGAGAGTCT
CTCCCCTTTGGTGACAACTCATTCAAGGATTCCAGACACTTGAATTTCCTGACATCAGAA
CAAGCTCTGGCTGATTTTGCAGAGTTAATCAAACACTTGAAAAGAACAATCCCAGGAGCT
GAAAATCAACCTGTCATTGCCATAGGAGGCTCCTATGGTGGCATGCTTGCCGCCTGGTTT
AGGATGAAATATCCTCATATGGTAGTTGGAGCTCTTGCAGCTTCTGCCCCTATCTGGCAG
TTTGAGGATTTAGTACCTTGTGGTGTATTTATGAAGATCGTAACTACAGATTTTAGGAAA
AGCGGTCCACATTGTTCAGAGAGCATCCACAGGTCCTGGGATGCCATTAATCGACTCTCA
AATACTGGCAGTGGTTTGCAGTGGCTTACTGGAGCCCTTCACTTATGCAGCCCATTAACT
TCTCAGGACATCCAACATTTGAAAGACTGGATCTCTGAAACCTGGGTGAATCTGGCAATG
GTGGACTATCCTTATGCCTCTAACTTTTTACAGCCTTTGCCTGCTTGGCCTATCAAGGTA
GTGTGCCAGTATTTGAAAAATCCCAATGTATCTGATTCACTGCTGCTGCAGAATATTTTC
CAAGCTCTGAATGTATATTACAATTATTCGGGCCAGGTGAAATGCCTGAATATTTCAGAG
ACAGCAACTAGCAGTCTGGGAACACTGGGTTGGAGCTATCAGGCCTGCACAGAAGTAGTC
ATGCCCTTTTGTACTAATGGTGTCGATGACATGTTTGAACCTCACTCATGGAACTTAAAG
GAACTTTCTGATGACTGTTTTCAACAGTGGGGTGTGAGACCAAGGCCCTCCTGGATCACT
ACTATGTATGGAGGCAAAAACATTAGTTCACACACAAACATTGTTTTCAGCAATGGTGAA
CTAGACCCCTGGTCAGGAGGTGGAGTAACTAAGGATATCACAGACACTCTGGTTGCAGTC
ACCATCTCAGAGGGGGCCCACCACTTAGATCTCCGCACCAAGAATGCCTTGGATCCTATG
TCTGTGCTGTTAGCCCGCTCCTTGGAAGTTAGACATATGAAGAATTGGATCAGAGATTTC
TATGACAGTGCGGGAAAGCAGCAC<u>**TGA**</u>GAAACTTTTGATTGTTTTCAATTTCTTCTTTTA
TGTTCACACCACCACATTCCCATTCACTTTGATTTTCTACATGTAATTACCTTCTTTTGT
TTATCATTAGATTTGATGGGGCCAAAGTTGAGATAGAATAGAGGGTGATGACGGTAAGAG
CAAGTGTCCCATGAATGTGATTTCCTGGGTTCTCACTGTCCTTTGCACCACGTCTAGGAA
GAATCTTCTTGATAGCTCTCCCACACCATCAGTGGCCCTCATAACTGGAGTAGAGTTCCT
GGTTGCTTTTCATAAGAGGGAGAGTTACTTTC

FIGURE 86

MGRRALLLLLLSFLAPWATIALRPALRALGSLHLPTNPTSLPAVAKNYSVLYFQQKVDHF
GFNTVKTFNQRYLVADKYWKKNGGSILFYTGNEGDIIWFCNNTGFMWDVAEELKAMLVFA
EHRYYGESLPFGDNSFKDSRHLNFLTSEQALADFAELIKHLKRTIPGAENQPVIAIGGSY
GGMLAAWFRMKYPHMVVGALAASAPIWQFEDLVPCGVFMKIVTTDFRKSGPHCSESIHRS
WDAINRLSNTGSGLQWLTGALHLCSPLTSQDIQHLKDWISETWVNLAMVDYPYASNFLQP
LPAWPIKVVCQYLKNPNVSDSLLLQNIFQALNVYYNYSGQVKCLNISETATSSLGTLGWS
YQACTEVVMPFCTNGVDDMFEPHSWNLKELSDDCFQQWGVRPRPSWITTMYGGKNISSHT
NIVFSNGELDPWSGGGVTKDITDTLVAVTISEGAHHLDLRTKNALDPMSVLLARSLEVRH
MKNWIRDFYDSAGKQH

Signal sequence:
1-18

Transmembrane domain:
None

N-glycosylation site:
47-50, 101-104, 317-320, 336-339, 345-348, 415-418

Glycosaminoglycan attachment site:
433-436

N-myristoylation site:
178-183, 181-186, 182-187, 198-203, 339-344, 434-439

Amidation site:
1-4

alpha/beta hydrolase fold:
115-372

FIGURE 87

GGCGGCGTCCGTGAGGGGCTCCTTTGGGCAGGGGTAGTGTTTGGTGTCCCTGTCTTGCGT
GATATTGACAAACTGAAGCTTTCCTGCACCACTGGACTTAAGGAAGAGTGTACTCGTAGG
CGGACAGCTTTAGTGGCCGGCCGGCCGCTCTCATCCCCCGTAAGGAGCAGAGTCCTTTGT
ACTGACCAAG**ATG**AGCAACATCTACATCCAGGAGCCTCCCACGAATGGGAAGGTTTTATT
GAAAACTACAGCTGGAGATATTGACATAGAGTTGTGGTCCAAAGAAGCTCCTAAAGCTTG
CAGAAATTTTATCCAACTTTGTTTGGAAGCTTATTATGACAATACCATTTTTCATAGAGT
TGTGCCTGGTTTCATAGTCCAAGGCGGAGATCCTACTGGCACAGGGAGTGGTGGAGAGTC
TATCTATGGAGCGCCATTCAAAGATGAATTTCATTCACGGTTGCGTTTTAATCGGAGAGG
ACTGGTTGCCATGGCAAATGCTGGTTCTCATGATAATGGCAGCCAGTTTTTCTTCACACT
GGGTCGAGCAGATGAACTTAACAATAAGCATACCATCTTTGGAAAGGTTACAGGGGATAC
AGTATATAACATGTTGCGACTGTCAGAAGTAGACATTGATGATGACGAAAGACCACATAA
TCCACACAAAATAAAAAGCTGTGAGGTTTTGTTTAATCCTTTTGATGACATCATTCCAAG
GGAAATTAAAAGGCTGAAAAAAGAGAAACCAGAGGAGGAAGTAAAGAAATTGAAACCCAA
AGGCACAAAAAATTTTAGTTTACTTTCATTTGGAGAGGAAGCTGAGGAAGAAGAGGAGGA
AGTAAATCGAGTTAGTCAGAGCATGAAGGGCAAAAGCAAAAGTAGTCATGACTTGCTTAA
GGATGATCCACATCTCAGTTCTGTTCCAGTTGTAGAAAGTGAAAAAGGTGATGCACCAGA
TTTAGTTGATGATGGAGAAGATGAAAGTGCAGAGCATGATGAATATATTGATGGTGATGA
AAAGAACCTGATGAGAGAAAGAATTGCCAAAAAATTAAAAAAGGACACAAGTGCGAATGT
TAAATCAGCTGGAGAAGGAGAAGTGGAGAAGAAATCAGTCAGCCGCAGTGAAGAGCTCAG
AAAAGAAGCAAGACAATTAAAACGGGAACTCTTAGCAGCAAAACAAAAAAAAAGTAGAAAA
TGCAGCAAAACAAGCAGAAAAAAGAAGTGAAGAGGAAGAAGCCCCTCCAGATGGTGCTGT
TGCCGAATACAGAAGAGAAAAGCAAAAGTATGAAGCTTTGAGGAAGCAACAGTCAAAGAA
GGGAACTTCCCGGGAAGATCAGACCCTTGCACTGCTGAACCAGTTTAAATCTAAACTCAC
TCAAGCAATTGCTGAAACACCTGAAAATGACATTCCTGAAACAGAAGTAGAAGATGATGA
AGGATGGATGTCACATGTACTTCAGTTTGAGGATAAAAGCAGAAAAGTGAAAGATGCAAG
CATGCAAGACTCAGATACATTTGAAATCTATGATCCTCGGAATCCAGTGAATAAAAGAAG
GAGGGAAGAAAGCAAAAAGCTGATGAGAGAGAAAAAAGAAAGAAGA**TAA**AATGAGAATAA
TGATAACCAGAACTTGCTGGAAATGTGCCTACAATGGCCTTGTAACAGCCATTGTTCCCA
ACAGCATCACTTAGGGGTGTGAAAAGAAGTATTTTTGAACCTGTTGTCTGGTTTTGAAAA
ACAATTATCTTGTTTTGCAAATTGTGGAATGATGTAAGCAAATGCTTTTGGTTACTGGTA
CATGTGTTTTTTCCTAGCTGACCTTTTATATTGCTAAATCTGAAATAAAATAACTTTCCT
TCCACAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 88

MSNIYIQEPPTNGKVLLKTTAGDIDIELWSKEAPKACRNFIQLCLEAYYDNTIFHRVVPG
FIVQGGDPTGTGSGGESIYGAPFKDEFHSRLRFNRRGLVAMANAGSHDNGSQFFFTLGRA
DELNNKHTIFGKVTGDTVYNMLRLSEVDIDDDERPHNPHKIKSCEVLFNPFDDIIPREIK
RLKKEKPEEEVKKLKPKGTKNFSLLSFGEEAEEEEEEVNRVSQSMKGKSKSSHDLLKDDP
HLSSVPVVESEKGDAPDLVDDGEDESAEHDEYIDGDEKNLMRERIAKKLKKDTSANVKSA
GEGEVEKKSVSRSEELRKEARQLKRELLAAKQKKVENAAKQAEKRSEEEEAPPDGAVAEY
RREKQKYEALRKQQSKKGTSREDQTLALLNQFKSKLTQAIAETPENDIPETEVEDDEGWM
SHVLQFEDKSRKVKDASMQDSDTFEIYDPRNPVNKRRREESKKLMREKKERR

Important features:
Signal peptide:
amino acids 1-21

N-glycosylation sites:
amino acids 109-112 and 201-204

Cyclophilin-type peptidyl-prolyl cis-trans isomerase signature:
amino acids 49-66

Homologous region to Cyclophilin-type peptidyl-prolyl cis-trans isomerase:
amino acids 96-140, 49-89 and 22-51

FIGURE 89

CCCGGCTCCGCTCCCTCTGCCCCCTCGGGGTCGCGCGCCCACG**ATG**CTGCAGGGCCCTGG
CTCGCTGCTGCTGCTCTTCCTCGCCTCGCACTGCTGCCTGGGCTCGGCGCGCGGGCTCTT
CCTCTTTGGCCAGCCCGACTTCTCCTACAAGCGCAGCAATTGCAAGCCCATCCCGGTCAA
CCTGCAGCTGTGCCACGGCATCGAATACCAGAACATGCGGCTGCCCAACCTGCTGGGCCA
CGAGACCATGAAGGAGGTGCTGGAGCAGGCCGGCGCTTGGATCCCGCTGGTCATGAAGCA
GTGCCACCCGGACACCAAGAAGTTCCTGTGCTCGCTCTTCGCCCCCGTCTGCCTCGATGA
CCTAGACGAGACCATCCAGCCATGCCACTCGCTCTGCGTGCAGGTGAAGGACCGCTGCGC
CCCGGTCATGTCCGCCTTCGGCTTCCCCTGGCCCGACATGCTTGAGTGCGACCGTTTCCC
CCAGGACAACGACCTTTGCATCCCCCTCGCTAGCAGCGACCACCTCCTGCCAGCCACCGA
GGAAGCTCCAAAGGTATGTGAAGCCTGCAAAAATAAAAATGATGATGACAACGACATAAT
GGAAACGCTTTGTAAAAATGATTTTGCACTGAAAATAAAAGTGAAGGAGATAACCTACAT
CAACCGAGATACCAAAATCATCCTGGAGACCAAGAGCAAGACCATTTACAAGCTGAACGG
TGTGTCCGAAAGGGACCTGAAGAAATCGGTGCTGTGGCTCAAAGACAGCTTGCAGTGCAC
CTGTGAGGAGATGAACGACATCAACGCGCCCTATCTGGTCATGGGACAGAAACAGGGTGG
GGAGCTGGTGATCACCTCGGTGAAGCGGTGGCAGAAGGGGCAGAGAGAGTTCAAGCGCAT
CTCCCGCAGCATCCGCAAGCTGCAGTGC**TAG**TCCCGGCATCCTGATGGCTCCGACAGGCC
TGCTCCAGAGCACGGCTGACCATTTCTGCTCCGGGATCTCAGCTCCCGTTCCCCAAGCAC
ACTCCTAGCTGCTCCAGTCTCAGCCTGGGCAGCTTCCCCCTGCCTTTTGCACGTTTGCAT
CCCCAGCATTTCCTGAGTTATAAGGCCACAGGAGTGGATAGCTGTTTTCACCTAAAGGAA
AAGCCCACCCGAATCTTGTAGAAATATTCAAACTAATAAAATCATGAATATTTTAA

FIGURE 90

MLQGPGSLLLLFLASHCCLGSARGLFLFGQPDFSYKRSNCKPIPVNLQLCHGIEYQNMRL
PNLLGHETMKEVLEQAGAWIPLVMKQCHPDTKKFLCSLFAPVCLDDLDETIQPCHSLCVQ
VKDRCAPVMSAFGFPWPDMLECDRFPQDNDLCIPLASSDHLLPATEEAPKVCEACKNKND
DDNDIMETLCKNDFALKIKVKEITYINRDTKIILETKSKTIYKLNGVSERDLKKSVLWLK
DSLQCTCEEMNDINAPYLVMGQKQGGELVITSVKRWQKGQREFKRISRSIRKLQC

Important features:
Signal peptide:
amino acids 1-20

Cysteine rich domain, homolgous to frizzled N terminus:
amino acids 6-153

FIGURE 91

GGAAGGGGAGGAGCAGGCCACACAGGCACAGGCCGGTGAGGGACCTGCCCAGACCTGGAG
GGTCTCGCTCTGTCACACAGGCTGGAGTGCAGTGGTGTGATCTTGGCTCATCGTAACCTC
CACCTCCCGGGTTCAAGTGATTCTCATGCCTCAGCCTCCCGAGTAGCTGGGATTACAGGT
GGTGACTTCCAAGAGTGACTCCGTCGGAGGAAA**ATG**ACTCCCCAGTCGCTGCTGCAGACG
ACACTGTTCCTGCTGAGTCTGCTCTTCCTGGTCCAAGGTGCCCACGGCAGGGGCCACAGG
GAAGACTTTCGCTTCTGCAGCCAGCGGAACCAGACACACAGGAGCAGCCTCCACTACAAA
CCCACACCAGACCTGCGCATCTCCATCGAGAACTCCGAAGAGGCCCTCACAGTCCATGCC
CCTTTCCCTGCAGCCCACCCTGCTTCCCGATCCTTCCCTGACCCCAGGGGCCTCTACCAC
TTCTGCCTCTACTGGAACCGACATGCTGGGAGATTACATCTTCTCTATGGCAAGCGTGAC
TTCTTGCTGAGTGACAAAGCCTCTAGCCTCCTCTGCTTCCAGCACCAGGAGGAGAGCCTG
GCTCAGGGCCCCCCGCTGTTAGCCACTTCTGTCACCTCCTGGTGGAGCCCTCAGAACATC
AGCCTGCCCAGTGCCGCCAGCTTCACCTTCTCCTTCCACAGTCCTCCCCACACGGCCGCT
CACAATGCCTCGGTGGACATGTGCGAGCTCAAAAGGGACCTCCAGCTGCTCAGCCAGTTC
CTGAAGCATCCCCAGAAGGCCTCAAGGAGGCCCTCGGCTGCCCCCGCCAGCCAGCAGTTG
CAGAGCCTGGAGTCGAAACTGACCTCTGTGAGATTCATGGGGGACATGGTGTCCTTCGAG
GAGGACCGGATCAACGCCACGGTGTGGAAGCTCCAGCCCACAGCCGGCCTCCAGGACCTG
CACATCCACTCCCGGCAGGAGGAGGAGCAGAGCGAGATCATGGAGTACTCGGTGCTGCTG
CCTCGAACACTCTTCCAGAGGACGAAAGGCCGGAGCGGGGAGGCTGAGAAGAGACTCCTC
CTGGTGGACTTCAGCAGCCAAGCCCTGTTCCAGGACAAGAATTCCAGCCAAGTCCTGGGT
GAGAAGGTCTTGGGGATTGTGGTACAGAACACCAAAGTAGCCAACCTCACGGAGCCCGTG
GTGCTCACTTTCCAGCACCAGCTACAGCCGAAGAATGTGACTCTGCAATGTGTGTTCTGG
GTTGAAGACCCCACATTGAGCAGCCCGGGGCATTGGAGCAGTGCTGGGTGTGAGACCGTC
AGGAGAGAAACCCAAACATCCTGCTTCTGCAACCACTTGACCTACTTTGCAGTGCTGATG
GTCTCCTCGGTGGAGGTGGACGCCGTGCACAAGCACTACCTGAGCCTCCTCTCCTACGTG
GGCTGTGTCGTCTCTGCCCTGGCCTGCCTTGTCACCATTGCCGCCTACCTCTGCTCCAGG
GTGCCCCTGCCGTGCAGGAGGAAACCTCGGGACTACACCATCAAGGTGCACATGAACCTG
CTGCTGGCCGTCTTCCTGCTGGACACGAGCTTCCTGCTCAGCGAGCCGGTGGCCCTGACA
GGCTCTGAGGCTGGCTGCCGAGCCAGTGCCATCTTCCTGCACTTCTCCCTGCTCACCTGC
CTTTCCTGGATGGGCCTCGAGGGGTACAACCTCTACCGACTCGTGGTGGAGGTCTTTGGC
ACCTATGTCCCTGGCTACCTACTCAAGCTGAGCGCCATGGGCTGGGGCTTCCCCATCTTT
CTGGTGACGCTGGTGGCCCTGGTGGATGTGGACAACTATGGCCCCATCATCTTGGCTGTG
CATAGGACTCCAGAGGGCGTCATCTACCCTTCCATGTGCTGGATCCGGGACTCCCTGGTC
AGCTACATCACCAACCTGGGCCTCTTCAGCCTGGTGTTTCTGTTCAACATGGCCATGCTA
GCCACCATGGTGGTGCAGATCCTGCGGCTGCGCCCCCACACCCAAAAGTGGTCACATGTG
CTGACACTGCTGGGCCTCAGCCTGGTCCTTGGCCTGCCCTGGGCCTTGATCTTCTTCTCC
TTTGCTTCTGGCACCTTCCAGCTTGTCGTCCTCTACCTTTTCAGCATCATCACCTCCTTC
CAAGGCTTCCTCATCTTCATCTGGTACTGGTCCATGCGGCTGCAGGCCCGGGGTGGCCCC
TCCCCTCTGAAGAGCAACTCAGACAGCGCCAGGCTCCCCATCAGCTCGGGCAGCACCTCG
TCCAGCCGCATC**TAG**GCCTCCAGCCCACCTGCCCATGTGATGAAGCAGAGATGCGGCCTC
GTCGCACACTGCCTGTGGCCCCCGAGCCAGGCCCAGCCCCAGGCCAGTCAGCCGCAGACT
TTGGAAAGCCCAACGACCATGGAGAGATGGGCCGTTGCCATGGTGGACGGACTCCCGGGC
TGGGCTTTTGAATTGGCCTTGGGGACTACTCGGCTCTCACTCAGCTCCCACGGGACTCAG
AAGTGCGCCGCCATGCTGCCTAGGGTACTGTCCCCACATCTGTCCCAACCCAGCTGGAGG
CCTGGTCTCTCCTTACAACCCCTGGGCCCAGCCCTCATTGCTGGGGGCCAGGCCTTGGAT
CTTGAGGGTCTGGCACATCCTTAATCCTGTGCCCCTGCCTGGGACAGAAATGTGGCTCCA
GTTGCTCTGTCTCTCGTGGTCACCCTGAGGGCACTCTGCATCCTCTGTCATTTTAACCTC
AGGTGGCACCCAGGGCGAATGGGGCCCAGGGCAGACCTTCAGGGCCAGAGCCCTGGCGGA

GGAGAGGCCCTTTGCCAGGAGCACAGCAGCAGCTCGCCTACCTCTGAGCCCAGGCCCCCT
CCCTCCCTCAGCCCCCCAGTCCTCCCTCCATCTTCCCTGGGGTTCTCCTCCTCTCCCAGG
GCCTCCTTGCTCCTTCGTTCACAGCTGGGGGTCCCCGATTCCAATGCTGTTTTTTGGGGA
GTGGTTTCCAGGAGCTGCCTGGTGTCTGCTGTAAATGTTTGTCTACTGCACAAGCCTCGG
CCTGCCCCTGAGCCAGGCTCGGTACCGATGCGTGGGCTGGGCTAGGTCCCTCTGTCCATC
TGGGCCTTTGTATGAGCTGCATTGCCCTTGCTCACCCTGACCAAGCACACGCCTCAGAGG
GGCCCTCAGCCTCTCCTGAAGCCCTCTTGTGGCAAGAACTGTGGACCATGCCAGTCCCGT
CTGGTTTCCATCCCACCACTCCAAGGACTGAGACTGACCTCCTCTGGTGACACTGGCCTA
GAGCCTGACACTCTCCTAAGAGGTTCTCTCCAAGCCCCCAAATAGCTCCAGGCGCCCTCG
GCCGCCCATCATGGTTAATTCTGTCCAACAAACACACACGGGTAGATTGCTGGCCTGTTG
TAGGTGGTAGGGACACAGATGACCGACCTGGTCACTCCTCCTGCCAACATTCAGTCTGGT
ATGTGAGGCGTGCGTGAAGCAAGAACTCCTGGAGCTACAGGGACAGGGAGCCATCATTCC
TGCCTGGGAATCCTGGAAGACTTCCTGCAGGAGTCAGCGTTCAATCTTGACCTTGAAGAT
GGGAAGGATGTTCTTTTTACGTACCAATTCTTTTGTCTTTTGATATTAAAAAGAAGTACA
TGTTCATTGTAGAGAATTTGGAAACTGTAGAAGAGAATCAAGAAGAAAAATAAAAATCAG
CTGTTGTAATCGCCTAGCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 92

MTPQSLLQTTLFLLSLLFLVQGAHGRGHREDFRFCSQRNQTHRSSLHYKPTPDLRISIEN
SEEALTVHAPFPAAHPASRSFPDPRGLYHFCLYWNRHAGRLHLLYGKRDFLLSDKASSLL
CFQHQEESLAQGPPLLATSVTSWWSPQNISLPSAASFTFSFHSPPHTAAHNASVDMCELK
RDLQLLSQFLKHPQKASRRPSAAPASQQLQSLESKLTSVRFMGDMVSFEEDRINATVWKL
QPTAGLQDLHIHSRQEEEQSEIMEYSVLLPRTLFQRTKGRSGEAEKRLLLVDFSSQALFQ
DKNSSQVLGEKVLGIVVQNTKVANLTEPVVLTFQHQLQPKNVTLQCVFWVEDPTLSSPGH
WSSAGCETVRRETQTSCFCNHLTYFAVLMVSSVEVDAVHKHYLSLLSYVGCVVSALACLV
TIAAYLCSRVPLPCRRKPRDYTIKVHMNLLLAVFLLDTSFLLSEPVALTGSEAGCRASAI
FLHFSLLTCLSWMGLEGYNLYRLVVEVFGTYVPGYLLKLSAMGWGFPIFLVTLVALVDVD
NYGPIILAVHRTPEGVIYPSMCWIRDSLVSYITNLGLFSLVFLFNMAMLATMVVQILRLR
PHTQKWSHVLTLLGLSLVLGLPWALIFFSFASGTFQLVVLYLFSIITSFQGFLIFIWYWS
MRLQARGGPSPLKSNSDSARLPISSGSTSSSRI

Important features:
Signal peptide:
amino acids 1-25

Putative transmembrane domains:
amino acids 382-398, 402-420, 445-468, 473-491, 519-537, 568-590 and 634-657

Microbodies C-terminal targeting signal:
amino acids 691-693

cAMP- and cGMP-dependent protein kinase phosphorylation sites:
amino acids 198-201 and 370-373

N-glycosylation sites:
amino acids 39-42, 148-151, 171-174, 234-237, 303-306, 324-327 and 341-344

G-protein coupled receptors family 2 proteins:
amino acids 475-504

FIGURE 93

CCCACGCGTCCGAAGGCAGACAAAGGTTCATTTGTAAAGAAGCTCCTTCCAGCACCTCCT
CTCTTCTCCTTTTGCCCAAACTCACCCAGTGAGTGTGAGCATTTAAGAAGCATCCTCTGC
CAAGACCAAAAGGAAAGAAGAAAAAGGGCCAAAAGCCAAA<u>ATG</u>AAACTGATGGTACTTGT
TTTCACCATTGGGCTAACTTTGCTGCTAGGAGTTCAAGCCATGCCTGCAAATCGCCTCTC
TTGCTACAGAAAGATACTAAAAGATCACAACTGTCACAACCTTCCGGAAGGAGTAGCTGA
CCTGACACAGATTGATGTCAATGTCCAGGATCATTTCTGGGATGGGAAGGGATGTGAGAT
GATCTGTTACTGCAACTTCAGCGAATTGCTCTGCTGCCCAAAAGACGTTTTCTTTGGACC
AAAGATCTCTTTCGTGATTCCTTGCAACAATCAA<u>TGA</u>GAATCTTCATGTATTCTGGAGAA
CACCATTCCTGATTTCCCACAAACTGCACTACATCAGTATAACTGCATTTCTAGTTTCTA
TATAGTGCAATAGAGCATAGATTCTATAAATTCTTACTTGTCTAAGACAAGTAAATCTGT
GTTAAACAAGTAGTAATAAAAGTTAATTCAATCTAAAAAAAAAAAAA

FIGURE 94

MKLMVLVFTIGLTLLLGVQAMPANRLSCYRKILKDHNCHNLPEGVADLTQIDVNVQDHFW
DGKGCEMICYCNFSELLCCPKDVFFGPKISFVIPCNNQ

Important features:
Signal peptide:
amino acids 1-20

N-glycosylation site:
amino acids 72-76

Tyrosine kinase phosphorylation site:
amino acids 63-71

FIGURE 95

GAATTCCGGGCCCCAGGATGCCAACTTTGAATAGG**ATG**AAGACTACAACTTGTTCCCTTC
TCATCTGCATCTCCCTGCTCCAGCTGATGGTCCCAGTGAATACTGATGAGACCATAGAGA
TTATCGTGGAGAATAAGGTCAAGGAACTTCTTGCCAATCCAGCTAACTATCCCTCCACTG
TAACGAAGACTCTCTCTTGCACTAGTGTCAAGACTATGAACAGATGGGCCTCCTGCCCTG
CTGGGATGACTGCTACTGGGTGTGCTTGTGGCTTTGCCTGTGGATCTTGGGAGATCCAGA
GTGGAGATACTTGCAACTGCCTGTGCTTACTCGTTGACTGGACCACTGCCCGCTGCTGCC
AACTGTCC**TAA**GAATGAAGAGGTGGAGAACCCAGCTTTGATATGATGAATCTAACAAAAA
CTGCAGTCTCAATTTGGAAATCTGACTCATGTGCCTTTAAATGTGTTCATATTGCCCATT
TACCCTGCTTCTTGAAATGCTTCTTGAAAAATAAAGACAAATTTGCATGTG

FIGURE 96

MKTTTCSLLICISLLQLMVPVNTDETIEIIVENKVKELLANPANYPSTVTKTLSCTSVK
TMNRWASCPAGMTATGCACGFACGSWEIQSGDTCNCLCLLVDWTTARCCQLS

FIGURE 97

GAGGCAGAAAGGCAGAAAGGAGAAAATTCAGGATAACTCTCCTGAGGGGTGAGCCAAGCC
CTGCCATGTAGTGCACGCAGGACATCAACAAACACAGATAACAGGAAATGATCCATTCCC
TGTGGTCACTTATTCTAAAGGCCCCAACCTTCAAAGTTCAAGTAGTGAT**ATG**GATGACTC
CACAGAAAGGGAGCAGTCACGCCTTACTTCTTGCCTTAAGAAAAGAGAAGAAATGAAACT
GAAGGAGTGTGTTTCCATCCTCCCACGGAAGGAAAGCCCCTCTGTCCGATCCTCCAAAGA
CGGAAAGCTGCTGGCTGCAACCTTGCTGCTGGCACTGCTGTCTTGCTGCCTCACGGTGGT
GTCTTTCTACCAGGTGGCCGCCCTGCAAGGGGACCTGGCCAGCCTCCGGGCAGAGCTGCA
GGGCCACCACGCGGAGAAGCTGCCAGCAGGAGCAGGAGCCCCCAAGGCCGGCCTGGAGGA
AGCTCCAGCTGTCACCGCGGGACTGAAAATCTTTGAACCACCAGCTCCAGGAGAAGGCAA
CTCCAGTCAGAACAGCAGAAATAAGCGTGCCGTTCAGGGTCCAGAAGAAACAGTCACTCA
AGACTGCTTGCAACTGATTGCAGACAGTGAAACACCAACTATACAAAAAGGATCTTACAC
ATTTGTTCCATGGCTTCTCAGCTTTAAAAGGGGAAGTGCCCTAGAAGAAAAAGAGAATAA
AATATTGGTCAAAGAAACTGGTTACTTTTTTATATATGGTCAGGTTTTATATACTGATAA
GACCTACGCCATGGGACATCTAATTCAGAGGAAGAAGGTCCATGTCTTTGGGGATGAATT
GAGTCTGGTGACTTTGTTTCGATGTATTCAAAATATGCCTGAAACACTACCCAATAATTC
CTGCTATTCAGCTGGCATTGCAAAACTGGAAGAAGGAGATGAACTCCAACTTGCAATACC
AAGAGAAAATGCACAAATATCACTGGATGGAGATGTCACATTTTTTGGTGCATTGAAACT
GCTG**TGA**CCTACTTACACCATGTCTGTAGCTATTTTCCTCCCTTTCTCTGTACCTCTAAG
AAGAAAGAATCTAACTGAAAATACCAAAAAAAAAAAAAAAA

FIGURE 98

MDDSTEREQSRLTSCLKKREEMKLKECVSILPRKESPSVRSSKDGKLLAATLLLALLSCC
LTVVSFYQVAALQGDLASLRAELQGHHAEKLPAGAGAPKAGLEEAPAVTAGLKIFEPPAP
GEGNSSQNSRNKRAVQGPEETVTQDCLQLIADSETPTIQKGSYTFVPWLLSFKRGSALEE
KENKILVKETGYFFIYGQVLYTDKTYAMGHLIQRKKVHVFGDELSLVTLFRCIQNMPETL
PNNSCYSAGIAKLEEGDELQLAIPRENAQISLDGDVTFFGALKLL

Transmembrane domain:
amino acids 47-72

N-glycosylation site:
amino acids 124-127, 242-245

cAMP- and cGMP-dependent protein kinase phosphorylation site:
amino acids 33-36, 173-176

N-myristoylation site:
amino acids 96-101

TNF family proteins:
amino acids 172-206

FIGURE 99

GCGAGGTGGCGATCGCTGAGAGGCAGGAGGGCCGAGGCGGGCCTGGGAGGCGGCCCGGAG
GTGGGGCGCCGCTGGGGCCGGCCCGCACGGGCTTCATCTGAGGGCGCACGGCCCGCGACC
GAGCGTGCGGACTGGCCTCCCAAGCGTGGGGCGACAAGCTGCCGGAGCTGCA**ATG**GGCCG
CGGCTGGGGATTCTTGTTTGGCCTCCTGGGCGCCGTGTGGCTGCTCAGCTCGGGCCACGG
AGAGGAGCAGCCCCCGGAGACAGCGGCACAGAGGTGCTTCTGCCAGGTTAGTGGTTACTT
GGATGATTGTACCTGTGATGTTGAAACCATTGATAGATTTAATAACTACAGGCTTTTCCC
AAGACTACAAAAACTTCTTGAAAGTGACTACTTTAGGTATTACAAGGTAAACCTGAAGAG
GCCGTGTCCTTTCTGGAATGACATCAGCCAGTGTGGAAGAAGGGACTGTGCTGTCAAACC
ATGTCAATCTGATGAAGTTCCTGATGGAATTAAATCTGCGAGCTACAAGTATTCTGAAGA
AGCCAATAATCTCATTGAAGAATGTGAACAAGCTGAACGACTTGGAGCAGTGGATGAATC
TCTGAGTGAGGAAACACAGAAGGCTGTTCTTCAGTGGACCAAGCATGATGATTCTTCAGA
TAACTTCTGTGAAGCTGATGACATTCAGTCCCCTGAAGCTGAATATGTAGATTTGCTTCT
TAATCCTGAGCGCTACACTGGTTACAAGGGACCAGATGCTTGGAAAATATGGAATGTCAT
CTACGAAGAAAACTGTTTTAAGCCACAGACAATTAAAAGACCTTTAAATCCTTTGGCTTC
TGGTCAAGGGACAAGTGAAGAGAACACTTTTTACAGTTGGCTAGAAGGTCTCTGTGTAGA
AAAAAGAGCATTCTACAGACTTATATCTGGCCTACATGCAAGCATTAATGTGCATTTGAG
TGCAAGATATCTTTTACAAGAGACCTGGTTAGAAAAGAAATGGGGACACAACATTACAGA
ATTTCAACAGCGATTTGATGGAATTTTGACTGAAGGAGAAGGTCCAAGAAGGCTTAAGAA
CTTGTATTTTCTCTACTTAATAGAACTAAGGGCTTTATCCAAAGTGTTACCATTCTTCGA
GCGCCCAGATTTTCAACTCTTTACTGGAAATAAAATTCAGGATGAGGAAAACAAAATGTT
ACTTCTGGAAATACTTCATGAAATCAAGTCATTTCCTTTGCATTTTGATGAGAATTCATT
TTTTGCTGGGGATAAAAAAGAAGCACACAAACTAAAGGAGGACTTTCGACTGCATTTTAG
AAATATTTCAAGAATTATGGATTGTGTTGGTTGTTTTAAATGTCGTCTGTGGGGAAAGCT
TCAGACTCAGGGTTTGGGCACTGCTCTGAAGATCTTATTTTCTGAGAAATTGATAGCAAA
TATGCCAGAAAGTGGACCTAGTTATGAATTCCATCTAACCAGACAAGAAATAGTATCATT
ATTCAACGCATTTGGAAGAATTTCTACAAGTGTGAAAGAATTAGAAAACTTCAGGAACTT
GTTACAGAATATTCAT**TAA**AGAAAACAAGCTGATATGTGCCTGTTTCTGGACAATGGAGG
CGAAAGAGTGGAATTTCATTCAAAGGCATAATAGCAATGACAGTCTTAAGCCAAACATTT
TATATAAAGTTGCTTTTGTAAAGGAGAATTATATTGTTTTAAGTAAACACATTTTTAAAA
ATTGTGTTAAGTCTATGTATAATACTACTGTGAGTAAAAGTAATACTTTAATAATGTGGT
ACAAATTTTAAAGTTTAATATTGAATAAAAGGAGGATTATCAAATTAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 100

MGRGWGFLFGLLGAVWLLSSGHGEEQPPETAAQRCFCQVSGYLDDCTCDVETIDRFNNYR
LFPRLQKLLESDYFRYYKVNLKRPCPFWNDISQCGRRDCAVKPCQSDEVPDGIKSASYKY
SEEANNLIEECEQAERLGAVDESLSEETQKAVLQWTKHDDSSDNFCEADDIQSPEAEYVD
LLLNPERYTGYKGPDAWKIWNVIYEENCFKPQTIKRPLNPLASGQGTSEENTFYSWLEGL
CVEKRAFYRLISGLHASINVHLSARYLLQETWLEKKWGHNITEFQQRFDGILTEGEGPRR
LKNLYFLYLIELRALSKVLPFFERPDFQLFTGNKIQDEENKMLLLEILHEIKSFPLHFDE
NSFFAGDKKEAHKLKEDFRLHFRNISRIMDCVGCFKCRLWGKLQTQGLGTALKILFSEKL
IANMPESGPSYEFHLTRQEIVSLFNAFGRISTSVKELENFRNLLQNIH

Important features:
Signal peptide:
amino acids 1-23

N-glycosylation site:
amino acids 280-283 and 384-387

Amidation site:
amino acids 94-97

Glycosaminoglycan attachment site:
amino acids 20-23 and 223-226

Aminotransferases class-V pyridoxal-phosphate:
amino acids 216-222

Interleukin-7 proteins:
amino acids 338-343

FIGURE 101

GCCTAGCCAGGCCAAGA**ATG**CAATTGCCCCGGTGGTGGGAGCTGGGAGACCCCTGTGCTT
GGACGGGACAGGGTCGGGGGACACGCAGG**ATG**AGCCCCGCGACCACTGGCACATTCTTGC
TGACAGTGTACAGTATTTTCTCCAAGGTACACTCCGATCGGAATGTATACCCATCAGCAG
GTGTCCTCTTTGTTCATGTTTTGGAAAGAGAATATTTTAAGGGGGAATTTCCACCTTACC
CAAAACCTGGCGAGATTAGTAATGATCCCATAACATTTAATACAAATTTAATGGGTTACC
CAGACCGACCTGGATGGCTTCGATATATCCAAAGGACACCATATAGTGATGGAGTCCTAT
ATGGGTCCCCAACAGCTGAAAATGTGGGGAAGCCAACAATCATTGAGATAACTGCCTACA
ACAGGCGCACCTTTGAGACTGCAAGGCATAATTTGATAATTAATATAATGTCTGCAGAAG
ACTTCCCGTTGCCATATCAAGCAGAATTCTTCATTAAGAATATGAATGTAGAAGAAATGT
TGGCCAGTGAGGTTCTTGGAGACTTTCTTGGCGCAGTGAAAAATGTGTGGCAGCCAGAGC
GCCTGAACGCCATAAACATCACATCGGCCCTAGACAGGGGTGGCAGGGTGCCACTTCCCA
TTAATGACCTGAAGGAGGGCGTTTATGTCATGGTTGGTGCAGATGTCCCGTTTTCTTCTT
GTTTACGAGAAGTTGAAAATCCACAGAATCAATTGAGATGTAGTCAAGAAATGGAGCCTG
TAATAACATGTGATAAAAAATTTCGTACTCAATTTTACATTGACTGGTGCAAAATTTCAT
TGGTTGATAAAACAAAGCAAGTGTCCACCTATCAGGAAGTGATTCGTGGAGAGGGGATTT
TACCTGATGGTGGAGAATACAAACCCCCTTCTGATTCTTTGAAAAGCAGAGACTATTACA
CGGATTTCCTAATTACACTGGCTGTGCCCTCGGCAGTGGCACTGGTCCTTTTTCTAATAC
TTGCTTATATCATGTGCTGCCGACGGGAAGGCGTGGAAAAGAGAAACATGCAAACACCAG
ACATCCAACTGGTCCATCACAGTGCTATTCAGAAATCTACCAAGGAGCTTCGAGACATGT
CCAAGAATAGAGAGATAGCATGGCCCCTGTCAACGCTTCCTGTGTTCCACCCTGTGACTG
GGGAAATCATACCTCCTTTACACACAGACAACTATGATAGCACAAACATGCCATTGATGC
AAACGCAGCAGAACTTGCCACATCAGACTCAGATTCCCCAACAGCAGACTACAGGTAAAT
GGTATCCC**TGA**AGAAAGAAAACTGACTGAAGCAATGAATTTATAATCAGACAATATAGCA
GTTACATCACATTTCTTTTCTCTTCCAATAATGCATGAGCTTTTCTGGCATATGTTATGC
ATGTTGGCAGTATTAAGTGTATACCAAATAATACAACATAACTTTCATTTTACTAATGTA
TTTTTTTGTACTTAAAGCATTTTTGACAATTTGTAAAACATTGATGACTTTATATTTGTT
ACAATAAAAGTTGATCTTTAAAATAAATATTATTAATGAAGCCTAAAAAAAAAAA

FIGURE 102

MQLPRWWELGDPCAWTGQGRGTRRMSPATTGTFLLTVYSIFSKVHSDRNVYPSAGVLFVH
VLEREYFKGEFPPYPKPGEISNDPITFNTNLMGYPDRPGWLRYIQRTPYSDGVLYGSPTA
ENVGKPTIIEITAYNRRTFETARHNLIINIMSAEDFPLPYQAEFFIKNMNVEEMLASEVL
GDFLGAVKNVWQPERLNAINITSALDRGGRVPLPINDLKEGVYVMVGADVPFSSCLREVE
NPQNQLRCSQEMEPVITCDKKFRTQFYIDWCKISLVDKTKQVSTYQEVIRGEGILPDGGE
YKPPSDSLKSRDYYTDFLITLAVPSAVALVLFLILAYIMCCRREGVEKRNMQTPDIQLVH
HSAIQKSTKELRDMSKNREIAWPLSTLPVFHPVTGEIIPPLHTDNYDSTNMPLMQTQQNL
PHQTQIPQQQTTGKWYP

signal sequence:
Amino acids 1-46

transmembrane domain:
Amino acids 319-338

N-glycosylation site:
Amino acids 200-204

cAMP- and cGMP-dependent protein kinase phosphorylation site:
Amino acids 23-27

Tyrosine kinase phosphorylation site:
Amino acids 43-52

N-myristoylation sites:
Amino acids 17-23;112-118;116-122;185-191

FIGURE 103

CAGAAGAGGGGGCTAGCTAGCTGTCTCTGCGGACCAGGGAGACCCCCGCGCCCCCCCGGT
GTGAGGCGGCCTCACAGGGCCGGGTGGGCTGGCGAGCCGACGCGGCGGCGGAGGAGGCTG
TGAGGAGTGTGTGGAACAGGACCCGGGACAGAGGAACC**ATG**GCTCCGCAGAACCTGAGCA
CCTTTTGCCTGTTGCTGCTATACCTCATCGGGGCGGTGATTGCCGGACGAGATTTCTATA
AGATCTTGGGGGTGCCTCGAAGTGCCTCTATAAAGGATATTAAAAAGGCCTATAGGAAAC
TAGCCCTGCAGCTTCATCCCGACCGGAACCCTGATGATCCACAAGCCCAGGAGAAATTCC
AGGATCTGGGTGCTGCTTATGAGGTTCTGTCAGATAGTGAGAAACGGAAACAGTACGATA
CTTATGGTGAAGAAGGATTAAAAGATGGTCATCAGAGCTCCCATGGAGACATTTTTTCAC
ACTTCTTTGGGGATTTTGGTTTCATGTTTGGAGGAACCCCTCGTCAGCAAGACAGAAATA
TTCCAAGAGGAAGTGATATTATTGTAGATCTAGAAGTCACTTTGGAAGAAGTATATGCAG
GAAATTTTGTGGAAGTAGTTAGAAACAAACCTGTGGCAAGGCAGGCTCCTGGCAAACGGA
AGTGCAATTGTCGGCAAGAGATGCGGACCACCCAGCTGGGCCCTGGGCGCTTCCAAATGA
CCCAGGAGGTGGTCTGCGACGAATGCCCTAATGTCAAACTAGTGAATGAAGAACGAACGC
TGGAAGTAGAAATAGAGCCTGGGGTGAGAGACGGCATGGAGTACCCCTTTATTGGAGAAG
GTGAGCCTCACGTGGATGGGGAGCCTGGAGATTTACGGTTCCGAATCAAAGTTGTCAAGC
ACCCAATATTTGAAAGGAGAGGAGATGATTTGTACACAAATGTGACAATCTCATTAGTTG
AGTCACTGGTTGGCTTTGAGATGGATATTACTCACTTGGATGGTCACAAGGTACATATTT
CCCGGGATAAGATCACCAGGCCAGGAGCGAAGCTATGGAAGAAAGGGGAAGGGCTCCCCA
ACTTTGACAACAACAATATCAAGGGCTCTTTGATAATCACTTTTGATGTGGATTTTCCAA
AAGAACAGTTAACAGAGGAAGCGAGAGAAGGTATCAAACAGCTACTGAAACAAGGGTCAG
TGCAGAAGGTATACAATGGACTGCAAGGATAT**TGA**GAGTGAATAAAATTGGACTTTGTTT
AAAATAAGTGAATAAGCGATATTTATTATCTGCAAGGTTTTTTTGTGTGTGTTTTTGTTT
TTATTTTCAATATGCAAGTTAGGCTTAATTTTTTTATCTAATGATCATCATGAAATGAAT
AAGAGGGCTTAAGAATTTGTCCATTTGCATTCGGAAAAGAATGACCAGCAAAAGGTTTAC
TAATACCTCTCCCTTTGGGGATTTAATGTCTGGTGCTGCCGCCTGAGTTTCAAGAATTAA
AGCTGCAAGAGGACTCCAGGAGCAAAAGAAACACAATATAGAGGGTTGGAGTTGTTAGCA
ATTTCATTCAAAATGCCAACTGGAGAAGTCTGTTTTTAAATACATTTTGTTGTTATTTTA

FIGURE 104

MAPQNLSTFCLLLLYLIGAVIAGRDFYKILGVPRSASIKDIKKAYRKLALQLHPDRNPDD
PQAQEKFQDLGAAYEVLSDSEKRKQYDTYGEEGLKDGHQSSHGDIFSHFFGDFGFMFGGT
PRQQDRNIPRGSDIIVDLEVTLEEVYAGNFVEVVRNKPVARQAPGKRKCNCRQEMRTTQL
GPGRFQMTQEVVCDECPNVKLVNEERTLEVEIEPGVRDGMEYPFIGEGEPHVDGEPGDLR
FRIKVVKHPIFERRGDDLYTNVTISLVESLVGFEMDITHLDGHKVHISRDKITRPGAKLW
KKGEGLPNFDNNNIKGSLIITFDVDFPKEQLTEEAREGIKQLLKQGSVQKVYNGLQGY

Important features:
Signal peptide:
amino acids 1-22

Cell attachment sequence:
amino acids 254-257

Nt-dnaJ domain signature:
amino acids 67-87

Homologous region to Nt-dnaJ domain proteins:
amino acids 26-58

N-glycosylation site:
amino acids 5-9, 261-265

Tyrosine kinase phosphorylation site:
amino acids 253-260

N-myristoylation site:
amino acids 18-24, 31-37, 93-99, 215-221

Amidation site:
amino acids 164-168

FIGURE 105

GGCACGAGGCGGCGGGGCAGTCGCGGGATGCGCCCGGGAGCCACAGCCTGAGGCCCTCAG
GTCTCTGCAGGTGTCGTGGAGGAACCTAGCACCTGCCATCCTCTTCCCCAATTTGCCACT
TCCAGCAGCTTTAGCCCATGAGGAGGATGTGACCGGGACTGAGTCAGGAGCCCTCTGGAA
GC**ATG**GAGACTGTGGTGATTGTTGCCATAGGTGTGCTGGCCACCATCTTTCTGGCTTCGT
TTGCAGCCTTGGTGCTGGTTTGCAGGCAGCGCTACTGCCGGCCGCGAGACCTGCTGCAGC
GCTATGATTCTAAGCCCATTGTGGACCTCATTGGTGCCATGGAGACCCAGTCTGAGCCCT
CTGAGTTAGAACTGGACGATGTCGTTATCACCAACCCCCACATTGAGGCCATTCTGGAGA
ATGAAGACTGGATCGAAGATGCCTCGGGTCTCATGTCCCACTGCATTGCCATCTTGAAGA
TTTGTCACACTCTGACAGAGAAGCTTGTTGCCATGACAATGGGCTCTGGGGCCAAGATGA
AGACTTCAGCCAGTGTCAGCGACATCATTGTGGTGGCCAAGCGGATCAGCCCCAGGGTGG
ATGATGTTGTGAAGTCGATGTACCCTCCGTTGGACCCCAAACTCCTGGACGCACGGACGA
CTGCCCTGCTCCTGTCTGTCAGTCACCTGGTGCTGGTGACAAGGAATGCCTGCCATCTGA
CGGGAGGCCTGGACTGGATTGACCAGTCTCTGTCGGCTGCTGAGGAGCATTTGGAAGTCC
TTCGAGAAGCAGCCCTAGCTTCTGAGCCAGATAAAGGCCTCCCAGGCCCTGAAGGCTTCC
TGCAGGAGCAGTCTGCAATT**TAG**TGCCTACAGGCCAGCAGCTAGCCATGAAGGCCCCTGC
CGCCATCCCTGGATGGCTCAGCTTAGCCTTCTACTTTTTCCTATAGAGTTAGTTGTTCTC
CACGGCTGGAGAGTTCAGCTGTGTGTGCATAGTAAAGCAGGAGATCCCCGTCAGTTTATG
CCTCTTTTGCAGTTGCAAACTGTGGCTGGTGAGTGGCAGTCTAATACTACAGTTAGGGGA
GATGCCATTCACTCTCTGCAAGAGGAGTATTGAAAACTGGTGGACTGTCAGCTTTATTTA
GCTCACCTAGTGTTTTCAAGAAAATTGAGCCACCGTCTAAGAAATCAAGAGGTTTCACAT
TAAAATTAGAATTTCTGGCCTCTCTCGATCGGTCAGAATGTGTGGCAATTCTGATCTGCA
TTTTCAGAAGAGGACAATCAATTGAAACTAAGTAGGGGTTTCTTCTTTTGGCAAGACTTG
TACTCTCTCACCTGGCCTGTTTCATTTATTTGTATTATCTGCCTGGTCCCTGAGGCGTCT
GGGTCTCTCCTCTCCCTTGCAGGTTTGGGTTTGAAGCTGAGGAACTACAAAGTTGATGAT
TTCTTTTTTATCTTTATGCCTGCAATTTTACCTAGCTACCACTAGGTGGATAGTAAATTT
ATACTTATGTTTCCCTCAAAAAAAAAAAAAAA

FIGURE 106

METVVIVAIGVLATIFLASFAALVLVCRQRYCRPRDLLQRYDSKPIVDLIGAMETQSEPS
ELELDDVVITNPHIEAILENEDWIEDASGLMSHCIAILKICHTLTEKLVAMTMGSGAKMK
TSASVSDIIVVAKRISPRVDDVVKSMYPPLDPKLLDARTTALLLSVSHLVLVTRNACHLT
GGLDWIDQSLSAAEEHLEVLREAALASEPDKGLPGPEGFLQEQSAI

FIGURE 107

GCTTCATTTCTCCCGACTCAGCTTCCCACCCTGGGCTTTCCGAGGTGCTTTCGCCGCTGT
CCCCACCACTGCAGCC**ATG**ATCTCCTTAACGGACACGCAGAAAATTGGAATGGGATTAAC
AGGATTTGGAGTGTTTTTCCTGTTCTTTGGAATGATTCTCTTTTTTGACAAAGCACTACT
GGCTATTGGAAATGTTTTATTTGTAGCCGGCTTGGCTTTTGTAATTGGTTTAGAAAGAAC
ATTCAGATTCTTCTTCCAAAAACATAAAATGAAAGCTACAGGTTTTTTCTGGGTGGTGT
ATTTGTAGTCCTTATTGGTTGGCCTTTGATAGGCATGATCTTCGAAATTTATGGATTTTT
TCTCTTGTTCAGGGGCTTCTTTCCTGTCGTTGTTGGCTTTATTAGAAGAGTGCCAGTCCT
TGGATCCCTCCTAAATTTACCTGGAATTAGATCATTTGTAGATAAAGTTGGAGAAAGCAA
CAATATGGTA**TAA**CAACAAGTGAATTTGAAGACTCATTTAAAATATTGTGTTATTTATAA
AGTCATTTGAAGAATATTCAGCACAAAATTAAATTACATGAAATAGCTTGTAATGTTCTT
TACAGGAGTTTAAAACGTATAGCCTACAAAGTACCAGCAGCAAATTAGCAAAGAAGCAGT
GAAAACAGGCTTCTACTCAAGTGAACTAAGAAGAAGTCAGCAAGCAAACTGAGAGAGGTG
AAATCCATGTTAATGATGCTTAAGAAACTCTTGAAGGCTATTTGTGTTGTTTTTCCACAA
TGTGCGAAACTCAGCCATCCTTAGAGAACTGTGGTGCCTGTTTCTTTTCTTTTTATTTTG
AAGGCTCAGGAGCATCCATAGGCATTTGCTTTTTAGAAGTGTCCACTGCAATGGCAAAAA
TATTTCCAGTTGCACTGTATCTCTGGAAGTGATGCATGAATTCGATTGGATTGTGTCATT
TTAAAGTATTAAAACCAAGGAAACCCCAATTTTGATGTATGGATTACTTTTTTTTGNGCN
CAGGGCC

FIGURE 108

MISLTDTQKIGMGLTGFGVFFLFFGMILFFDKALLAIGNVLFVAGLAFVIGLERTFRFFF
QKHKMKATGFFLGGVFVVLIGWPLIGMIFEIYGFFLLFRGFFPVVVGFIRRVPVLGSLLN
LPGIRSFVDKVGESNNMV

Important features:
Transmembrane domains:
amino acids 12-30 (typeII), 33-52, 69-89 and 93-109

N-myristoylation sites:
amino acids 11-16, 51-56 and 116-121

Aminoacyl-transfer RNA synthetases class-II protein:
amino acids 49-59

FIGURE 109

CCAGTCTGTCGCCACCTCACTTGGTGTCTGCTGTCCCCGCCAGGCAAGCCTGGGGTGAGA
GCACAGAGGAGTGGGCCGGGACC<u>ATG</u>CGGGGGACGCGGCTGGCGCTCCTGGCGCTGGTGC
TGGCTGCCTGCGGAGAGCTGGCGCCGGCCCTGCGCTGCTACGTCTGTCCGGAGCCCACAG
GAGTGTCGGACTGTGTCACCATCGCCACCTGCACCACCAACGAAACCATGTGCAAGACCA
CACTCTACTCCCGGGAGATAGTGTACCCCTTCCAGGGGGACTCCACGGTGACCAAGTCCT
GTGCCAGCAAGTGTAAGCCCTCGGATGTGGATGGCATCGGCCAGACCCTGCCCGTGTCCT
GCTGCAATACTGAGCTGTGCAATGTAGACGGGGCGCCCGCTCTGAACAGCCTCCACTGCG
GGGCCCTCACGCTCCTCCCACTCTTGAGCCTCCGACTG**<u>TAG</u>**AGTCCCCGCCCACCCCCAT
GGCCCTATGCGGCCCAGCCCCGAATGCCTTGAAGAAGTGCCCCCTGCACCAGGAAAAAAA
AAAAAAAAAA

FIGURE 110

MRGTRLALLALVLAACGELAPALRCYVCPEPTGVSDCVTIATCTTNETMCKTTLYSREIV
YPFQGDSTVTKSCASKCKPSDVDGIGQTLPVSCCNTELCNVDGAPALNSLHCGALTLLPL
LSLRL

Important features:
Signal peptide:
amino acids 1-17

N-glycosylation site:
amino acids 46-49

FIGURE 111

GCGCCGCCAGGCGTAGGCGGGGTGGCCCTTGCGTCTCCCGCTTCCTTGAAAAACCCGGCG
GGCGAGCGAGGCTGCGGGCCGGCCGCTGCCCTTCCCCACACTCCCCGCCGAGAAGCCTCG
CTCGGCGCCCAAC<u>ATG</u>GCGGGTGGGCGCTGCGGCCCGCAGCTAACGGCGCTCCTGGCCGC
CTGGATCGCGGCTGTGGCGGCGACGGCAGGCCCCGAGGAGGCCGCGCTGCCGCCGGAGCA
GAGCCGGGTCCAGCCCATGACCGCCTCCAACTGGACGCTGGTGATGGAGGGCGAGTGGAT
GCTGAAATTTTACGCCCCATGGTGTCCATCCTGCCAGCAGACTGATTCAGAATGGGAGGC
TTTTGCAAAGAATGGTGAAATACTTCAGATCAGTGTGGGGAAGGTAGATGTCATTCAAGA
ACCAGGTTTGAGTGGCCGCTTCTTTGTCACCACTCTCCCAGCATTTTTTCATGCAAAGGA
TGGGATATTCCGCCGTTATCGTGGCCCAGGAATCTTCGAAGACCTGCAGAATTATATCTT
AGAGAAGAAATGGCAATCAGTCGAGCCTCTGACTGGCTGGAAATCCCCAGCTTCTCTAAC
GATGTCTGGAATGGCTGGTCTTTTTAGCATCTCTGGCAAGATATGGCATCTTCACAACTA
TTTCACAGTGACTCTTGGAATTCCTGCTTGGTGTTCTTATGTGTTTTTCGTCATAGCCAC
CTTGGTTTTTGGCCTTTTTATGGGTCTGGTCTTGGTGGTAATATCAGAATGTTTCTATGT
GCCACTTCCAAGGCATTTATCTGAGCGTTCTGAGCAGAATCGGAGATCAGAGGAGGCTCA
TAGAGCTGAACAGTTGCAGGATGCGGAGGAGGAAAAAGATGATTCAAATGAAGAAGAAAA
CAAAGACAGCCTTGTAGATGATGAAGAAGAGAAAGAAGATCTTGGCGATGAGGATGAAGC
AGAGGAAGAAGAGGAGGAGGACAACTTGGCTGCTGGTGTGGATGAGGAGAGAAGTGAGGC
CAATGATCAGGGGCCCCCAGGAGAGGACGGTGTGACCCGGGAGGAAGTAGAGCCTGAGGA
GGCTGAAGAAGGCATCTCTGAGCAACCCTGCCCAGCTGACACAGAGGTGGTGGAAGACTC
CTTGAGGCAGCGTAAAAGTCAGCATGCTGACAAGGGACTG<u>TAG</u>ATTTAATGATGCGTTTT
CAAGAATACACACCAAAACAATATGTCAGCTTCCCTTTGGCCTGCAGTTTGTACCAAATC
CTTAATTTTTCCTGAATGAGCAAGCTTCTCTTAAAAGATGCTCTCTAGTCATTTGGTCTC
ATGGCAGTAAGCCTCATGTATACTAAGGAGAGTCTTCCAGGTGTGACAATCAGGATATAG
AAAAACAAACGTAGTGTTGGGATCTGTTTGGAGACTGGGATGGGAACAAGTTCATTTACT
TAGGGGTCAGAGAGTCTCGACCAGAGGAGGCCATTCCCAGTCCTAATCAGCACCTTCCAG
AGACAAGGCTGCAGGCCCTGTGAAATGAAAGCCAAGCAGGAGCCTTGGCTCCTGAGCATC
CCCAAAGTGTAACGTAGAAGCCTTGCATCCTTTTCTTGTGTAAAGTATTTATTTTTGTCA
AATTGCAGGAAACATCAGGCACCACAGTGCATGAAAAATCTTTCACAGCTAGAAATTGAA
AGGGCCTTGGGTATAGAGAGCAGCTCAGAAGTCATCCCAGCCCTCTGAATCTCCTGTGCT
ATGTTTTATTTCTTACCTTTAATTTTTCCAGCATTTCCACCATGGGCATTCAGGCTCTCC
ACACTCTTCACTATTATCTCTTGGTCAGAGGACTCCAATAACAGCCAGGTTTACATGAAC
TGTGTTTGTTCATTCTGACCTAAGGGGTTTAGATAATCAGTAACCATAACCCCTGAAGCT
GTGACTGCCAAACATCTCAAATGAAATGTTGTGGCCATCAGAGACTCAAAAGGAAGTAAG
GATTTTACAAGACAGATTAAAAAAAAATTGTTTTGTCCAAAATATAGTTGTTGTTGATTT
TTTTTTAAGTTTTCTAAGCAATATTTTTCAAGCCAGAAGTCCTCTAAGTCTTGCCAGTAC
AAGGTAGTCTTGTGAAGAAAAGTTGAATACTGTTTTGTTTTCATCTCAAGGGGTTCCCTG
GGTCTTGAACTACTTTAATAATAACTAAAAAACCACTTCTGATTTTCCTTCAGTGATGTG
CTTTTGGTGAAAGAATTAATGAACTCCAGTACCTGAAAGTGAAAGATTTGATTTTGTTTC
CATCTTCTGTAATCTTCCAAAGAATTATATCTTTGTAAATCTCTCAATACTCAATCTACT
GTAAGTACCCAGGGAGGCTAATTTCTTT

FIGURE 112

MAGGRCGPQLTALLAAWIAAVAATAGPEEAALPPEQSRVQPMTASNWTLVMEGEWMLKFY
APWCPSCQQTDSEWEAFAKNGEILQISVGKVDVIQEPGLSGRFFVTTLPAFFHAKDGIFR
RYRGPGIFEDLQNYILEKKWQSVEPLTGWKSPASLTMSGMAGLFSISGKIWHLHNYFTVT
LGIPAWCSYVFFVIATLVFGLFMGLVLVVISECFYVPLPRHLSERSEQNRRSEEAHRAEQ
LQDAEEEKDDSNEEENKDSLVDDEEEKEDLGDEDEAEEEEEEDNLAAGVDEERSEANDQG
PPGEDGVTREEVEPEEAEEGISEQPCPADTEVVEDSLRQRKSQHADKGL

Important features:
Signal peptide:
amino acids 1-22

Transmembrane domain:
amino acids 191-211

N-glycosylation site:
amino acids 46-49

Thioredoxin family proteins: (homologous region to disulfide isomerase)
amino acids 56-72

Flavodoxin proteins:
amino acids 173-187

FIGURE 113

GAGGAACCTACCGGTACCGGCCGCGCGCTGGTAGTCGCCGGTGTGGCTGCACCTCACCAA
TCCCGTGCGCCGCGGCTGGGCCGTCGGAGAGTGCGTGTGCTTCTCTCCTGCACGCGGTGC
TTGGGCTCGGCCAGGCGGGGTCCGCCGCCAGGGTTTGAGGATGGGGGAGTAGCTACAGGA
AGCGACCCCGCGATGGCAAGGTATATTTTTGTGGAATGAAAAGGAAGTATTAGAAATGAG
CTGAAGACCATTCACAGATTAATATTTTTGGGGACAGATTTGTGATGCTTGATTCACCCT
TGAAGTAATGTAGACAGAAGTTCTCAAATTTGCATATTACATCAACTGGAACCAGCAGTG
AATCTTAATGTTCACTTAAATCAGAACTTGCATAAGAAAGAGAATGGGAGTCTGGTTAAA
TAAAGATGACTATATCAGAGACTTGAAAAGGATCATTCTCTGTTTTCTGATAGTGTATAT
GGCCATTTTAGTGGGCACAGATCAGGATTTTTACAGTTTACTTGGAGTGTCCAAAACTGC
AAGCAGTAGAGAAATAAGACAAGCTTTCAAGAAATTGGCATTGAAGTTACATCCTGATAA
AAACCCGAATAACCCAAATGCACATGGCGATTTTTTAAAAATAAATAGAGCATATGAAGT
ACTCAAAGATGAAGATCTACGGAAAAAGTATGACAAATATGGAGAAAAGGGACTTGAGGA
TAATCAAGGTGGCCAGTATGAAAGCTGGAACTATTATCGTTATGATTTTGGTATTTATGA
TGATGATCCTGAAATCATAACATTGGAAAGAAGAGAATTTGATGCTGCTGTTAATTCTGG
AGAACTGTGGTTTGTAAATTTTTACTCCCCAGGCTGTTCACACTGCCATGATTTAGCTCC
CACATGGAGAGACTTTGCTAAAGAAGTGGATGGGTTACTTCGAATTGGAGCTGTTAACTG
TGGTGATGATAGAATGCTTTGCCGAATGAAAGGAGTCAACAGCTATCCCAGTCTCTTCAT
TTTTCGGTCTGGAATGGCCCCAGTGAAATATCATGGAGACAGATCAAAGGAGAGTTTAGT
GAGTTTTGCAATGCAGCATGTTAGAAGTACAGTGACAGAACTTTGGACAGGAAATTTTGT
CAACTCCATACAAACTGCTTTTGCTGCTGGTATTGGCTGGCTGATCACTTTTTGTTCAAA
AGGAGGAGATTGTTTGACTTCACAGACACGACTCAGGCTTAGTGGCATGTTGTTTCTCAA
CTCATTGGATGCTAAAGAAATATATTTGGAAGTAATACATAATCTTCCAGATTTTGAACT
ACTTTCGGCAAACACACTAGAGGATCGTTTGGCTCATCATCGGTGGCTGTTATTTTTTCA
TTTTGGAAAAAATGAAAATTCAAATGATCCTGAGCTGAAAAAACTAAAAACTCTACTTAA
AAATGATCATATTCAAGTTGGCAGGTTTGACTGTTCCTCTGCACCAGACATCTGTAGTAA
TCTGTATGTTTTTCAGCCGTCTCTAGCAGTATTTAAAGGACAAGGAACCAAAGAATATGA
AATTCATCATGGAAAGAAGATTCTATATGATATACTTGCCTTTGCCAAAGAAAGTGTGAA
TTCTCATGTTACCACGCTTGGACCTCAAAATTTTCCTGCCAATGACAAAGAACCATGGCT
TGTTGATTTCTTTGCCCCCTGGTGTCCACCATGTCGAGCTTTACTACCAGAGTTACGAAG
AGCATCAAATCTTCTTTATGGTCAGCTTAAGTTTGGTACACTAGATTGTACAGTTCATGA
GGGACTCTGTAACATGTATAACATTCAGGCTTATCCAACAACAGTGGTATTCAACCAGTC
CAACATTCATGAGTATGAAGGACATCACTCTGCTGAACAAATCTTGGAGTTCATAGAGGA
TCTTATGAATCCTTCAGTGGTCTCCCTTACACCCACCACCTTCAACGAACTAGTTACACA
AAGAAAACACAACGAAGTCTGGATGGTTGATTTCTATTCTCCGTGGTGTCATCCTTGCCA
AGTCTTAATGCCAGAATGGAAAAGAATGGCCCGGACATTAACTGGACTGATCAACGTGGG
CAGTATAGATTGCCAACAGTATCATTCTTTTTGTGCCCAGGAAAACGTTCAAAGATACCC
TGAGATAAGATTTTTTCCCCCAAAATCAAATAAAGCTTATCAGTATCACAGTTACAATGG
TTGGAATAGGGATGCTTATTCCCTGAGAATCTGGGGTCTAGGATTTTTACCTCAAGTATC
CACAGATCTAACACCTCAGACTTTCAGTGAAAAAGTTCTACAAGGGAAAAATCATTGGGT
GATTGATTTCTATGCTCCTTGGTGTGGACCTTGCCAGAATTTTGCTCCAGAATTTGAGCT
CTTGGCTAGGATGATTAAAGGAAAAGTGAAAGCTGGAAAAGTAGACTGTCAGGCTTATGC
TCAGACATGCCAGAAAGCTGGGATCAGGGCCTATCCAACTGTTAAGTTTTATTTCTACGA
AAGAGCAAAGAGAAATTTTCAAGAAGAGCAGATAAATACCAGAGATGCAAAAGCAATCGC
TGCCTTAATAAGTGAAAAATTGGAAACTCTCCGAAATCAAGGCAAGAGGAATAAGGATGA
ACTTTGATAATGTTGAAGATGAAGAAAAAGTTTAAAAGAAATTCTGACAGATGACATCAG
AAGACACCTATTTAGAATGTTACATTTATGATGGGAATGAATGAACATTATCTTAGACTT

GCAGTTGTACTGCCAGAATTATCTACAGCACTGGTGTAAAAGAAGGGTCTGCAAACTTTT
TCTGTAAAGGGCCGGTTTATAAATATTTTAGACTTTGCAGGCTATAATATATGGTTCACA
CATGAGAACAAGAATAGAGTCATCATGTATTCTTTGTTATTTGCTTTTAACAACCTTTAA
AAAATATTAAAACGATTCTTAGCTCAGAGCCATACAAAAGTAGGCTGGATTCAGTCCATG
GACCATAGATTGCTGTCCCCCTCGACGGACTTATAATGTTTCAGGTGGCTGGCTTGAACA
TGAGTCTGCTGTGCTATCTACATAAATGTCTAAGTTGTATAAAGTCCACTTTCCCTTCAC
GTTTTTTGGCTGACCTGAAAAGAGGTAACTTAGTTTTTGGTCACTTGTTCTCCTAAAAAT
GCTATCCCTAACCATATATTTATATTTCGTTTTAAAAACACCCATGATGTGGCACAGTAA
ACAAACCCTGTTATGCTGTATTATTATGAGGAGATTCTTCATTGTTTTCTTTCCTTCTCA
AAGGTTGAAAAAAATGCTTTTAATTTTTCACAGCCGAGAAACAGTGCAGCAGTATATGTGC
ACACAGTAAGTACACAAATTTGAGCAACAGTAAGTGCACAAATTCTGTAGTTTGCTGTAT
CATCCAGGAAAACCTGAGGGAAAAAAATTATAGCAATTAACTGGGCATTGTAGAGTATCC
TAAATATGTTATCAAGTATTTAGAGTTCTATATTTTAAAGATATATGTGTTCATGTATTT
TCTGAAATTGCTTTCATAGAAATTTTCCCACTGATAGTTGATTTTTGAGGCATCTAATAT
TTACATATTTGCCTTCTGAACTTTGTTTTGACCTGTATCCTTTATTTACATTGGGTTTTT
CTTTCATAGTTTTGGTTTTTCACTCCTGTCCAGTCTATTTATTATTCAAATAGGAAAAAT
TACTTTACAGGTTGTTTTACTGTAGCTTATAATGATACTGTAGTTATTCCAGTTACTAGT
TTACTGTCAGAGGGCTGCCTTTTTCAGATAAATATTGACATAATAACTGAAGTTATTTTT
ATAAGAAAATCAAGTATATAAATCTAGGAAAGGGATCTTCTAGTTTCTGTGTTGTTTAGA
CTCAAAGAATCACAAATTTGTCAGTAACATGTAGTTGTTTAGTTATAATTCAGAGTGTAC
AGAATGGTAAAAATTCCAATCAGTCAAAAGAGGTCAATGAATTAAAAGGCTTGCAACTTT
TTCAAAAAAAAAAAAAAAAA

FIGURE 114

MGVWLNKDDYIRDLKRIILCFLIVYMAILVGTDQDFYSLLGVSKTASSREIRQAFKKLAL
KLHPDKNPNNPNAHGDFLKINRAYEVLKDEDLRKKYDKYGEKGLEDNQGGQYESWNYYRY
DFGIYDDDPEIITLERREFDAAVNSGELWFVNFYSPGCSHCHDLAPTWRDFAKEVDGLLR
IGAVNCGDDRMLCRMKGVNSYPSLFIFRSGMAPVKYHGDRSKESLVSFAMQHVRSTVTEL
WTGNFVNSIQTAFAAGIGWLITFCSKGGDCLTSQTRLRLSGMLFLNSLDAKEIYLEVIHN
LPDFELLSANTLEDRLAHHRWLLFFHFGKNENSNDPELKKLKTLLKNDHIQVGRFDCSSA
PDICSNLYVFQPSLAVFKGQGTKEYEIHHGKKILYDILAFAKESVNSHVTTLGPQNFPAN
DKEPWLVDFFAPWCPPCRALLPELRRASNLLYGQLKFGTLDCTVHEGLCNMYNIQAYPTT
VVFNQSNIHEYEGHHSAEQILEFIEDLMNPSVVSLTPTTFNELVTQRKHNEVWMVDFYSP
WCHPCQVLMPEWKRMARTLTGLINVGSIDCQQYHSFCAQENVQRYPEIRFFPPKSNKAYQ
YHSYNGWNRDAYSLRIWGLGFLPQVSTDLTPQTFSEKVLQGKNHWVIDFYAPWCGPCQNF
APEFELLARMIKGKVKAGKVDCQAYAQTCQKAGIRAYPTVKFYFYERAKRNFQEEQINTR
DAKAIAALISEKLETLRNQGKRNKDEL

Important features:
Endoplasmic reticulum targeting sequence:
amino acids 744-747

Cytochrome c family heme-binding site signature:
amino acids 158-163

Nt-dnaJ domain signature:
amino acids 77-96

N-glycosylation site:
amino acids 484-487

FIGURE 115

GCGGGCTGTTGACGGCGCTGCG**<u>ATG</u>**GCTGCCTGCGAGGGCAGGAGAAGCGGAGCTCTCGG
TTCCTCTCAGTCGGACTTCCTGACGCCGCCAGTGGGCGGGGCCCCTTGGGCCGTCGCCAC
CACTGTAGTCATGTACCCACCGCCGCCGCCGCCGCCTCATCGGGACTTCATCTCGGTGAC
GCTGAGCTTTGGCGAGAGCTATGACAACAGCAAGAGTTGGCGGCGGCGCTCGTGCTGGAG
GAAATGGAAGCAACTGTCGAGATTGCAGCGGAATATGATTCTCTTCCTCCTTGCCTTTCT
GCTTTTCTGTGGACTCCTCTTCTACATCAACTTGGCTGACCATTGGAAAGCTCTGGCTTT
CAGGCTAGAGGAAGAGCAGAAGATGAGGCCAGAAATTGCTGGGTTAAAACCAGCAAATCC
ACCCGTCTTACCAGCTCCTCAGAAGGCGGACACCGACCCTGAGAACTTACCTGAGATTTC
GTCACAGAAGACACAAAGACACATCCAGCGGGGACCACCTCACCTGCAGATTAGACCCCC
AAGCCAAGACCTGAAGGATGGGACCCAGGAGGAGGCCACAAAAAGGCAAGAAGCCCCTGT
GGATCCCCGCCCGGAAGGAGATCCGCAGAGGACAGTCATCAGCTGGAGGGGAGCGGTGAT
CGAGCCTGAGCAGGGCACCGAGCTCCCTTCAAGAAGAGCAGAAGTGCCCACCAAGCCTCC
CCTGCCACCGGCCAGGACACAGGGCACACCAGTGCATCTGAACTATCGCCAGAAGGGCGT
GATTGACGTCTTCCTGCATGCATGGAAAGGATACCGCAAGTTTGCATGGGGCCATGACGA
GCTGAAGCCTGTGTCCAGGTCCTTCAGTGAGTGGTTTGGCCTCGGTCTCACACTGATCGA
CGCGCTGGACACCATGTGGATCTTGGGTCTGAGGAAAGAATTTGAGGAAGCCAGGAAGTG
GGTGTCGAAGAAGTTACACTTTGAAAAGGACGTGGACGTCAACCTGTTTGAGAGCACGAT
CCGCATCCTGGGGGGGCTCCTGAGTGCCTACCACCTGTCTGGGGACAGCCTCTTCCTGAG
GAAAGCTGAGGATTTTGGAAATCGGCTAATGCCTGCCTTCAGAACACCATCCAAGATTCC
TTACTCGGATGTGAACATCGGTACTGGAGTTGCCCACCCGCCACGGTGGACCTCCGACAG
CACTGTGGCCGAGGTGACCAGCATTCAGCTGGAGTTCCGGGAGCTCTCCCGTCTCACAGG
GGATAAGAAGTTTCAGGAGGCAGTGGAGAAGGTGACACAGCACATCCACGGCCTGTCTGG
GAAGAAGGATGGGCTGGTGCCCATGTTCATCAATACCCACAGTGGCCTCTTCACCCACCT
GGGCGTATTCACGCTGGGCGCCAGGGCCGACAGCTACTATGAGTACCTGCTGAAGCAGTG
GATCCAGGGCGGGAAGCAGGAGACACAGCTGCTGGAAGACTACGTGGAAGCCATCGAGGG
TGTCAGAACGCACCTGCTGCGGCACTCCGAGCCCAGTAAGCTCACCTTTGTGGGGGAGCT
TGCCCACGGCCGCTTCAGTGCCAAGATGGACCACCTGGTGTGCTTCCTGCCAGGGACGCT
GGCTCTGGGCGTCTACCACGGCCTGCCCGCCAGCCACATGGAGCTGGCCCAGGAGCTCAT
GGAGACTTGTTACCAGATGAACCGGCAGATGGAGACGGGGCTGAGTCCCGAGATCGTGCA
CTTCAACCTTTACCCCCAGCCGGGCCGTCGGGACGTGGAGGTCAAGCCAGCAGACAGGCA
CAACCTGCTGCGGCCAGAGACCGTGGAGAGCCTGTTCTACCTGTACCGCGTCACAGGGGA
CCGCAAATACCAGGACTGGGGCTGGGAGATTCTGCAGAGCTTCAGCCGATTCACACGGGT
CCCCTCGGGTGGCTATTCTTCCATCAACAATGTCCAGGATCCTCAGAAGCCCGAGCCTAG
GGACAAGATGGAGAGCTTCTTCCTGGGGGAGACGCTCAAGTATCTGTTCTTGCTCTTCTC
CGATGACCCAAACCTGCTCAGCCTGGACGCCTACGTGTTCAACACCGAAGCCCACCCTCT
GCCTATCTGGACCCCTGCC**<u>TAG</u>**GGTGGATGGCTGCTGGTGTGGGGACTTCGGGTGGGCAG
AGGCACCTTGCTGGGTCTGTGGCATTTTCCAAGGGCCCACGTAGCACCGGCAACCGCCAA
GTGGCCCAGGCTCTGAACTGGCTCTGGGCTCCTCCTCGTCTCTGCTTTAATCAGGACACC
GTGAGGACAAGTGAGGCCGTCAGTCTTGGTGTGATGCGGGGTGGGCTGGGCCGCTGGAGC
CTCCGCCTGCTTCCTCCAGAAGACACGAATCATGACTCACGATTGCTGAAGCCTGAGCAG
GTCTCTGTGGGCCGACCAGAGGGGGGCTTCGAGGTGGTCCCTGGTACTGGGGTGACCGAG
TGGACAGCCCAGGGTGCAGCTCTGCCCGGGCTCGTGAAGCCTCAGATGTCCCCAATCCAA
GGGTCTGGAGGGGCTGCCGTGACTCCAGAGGCCTGAGGCTCCAGGGCTGGCTCTGGTGTT
TACAAGCTGGACTCAGGGATCCTCCTGGCCGCCCCGCAGGGGGCTTGGAGGGCTGGACGG
CAAGTCCGTCTAGCTCACGGGCCCCTCCAGTGGAATGGGTCTTTTCGGTGGAGATAAAAG
TTGATTTGCTCTAACCGCAA

FIGURE 116

MAACEGRRSGALGSSQSDFLTPPVGGAPWAVATTVVMYPPPPPPPHRDFISVTLSFGESY
DNSKSWRRRSCWRKWKQLSRLQRNMILFLLAFLLFCGLLFYINLADHWKALAFRLEEEQK
MRPEIAGLKPANPPVLPAPQKADTDPENLPEISSQKTQRHIQRGPPHLQIRPPSQDLKDG
TQEEATKRQEAPVDPRPEGDPQRTVISWRGAVIEPEQGTELPSRRAEVPTKPPLPPARTQ
GTPVHLNYRQKGVIDVFLHAWKGYRKFAWGHDELKPVSRSFSEWFGLGLTLIDALDTMWI
LGLRKEFEEARKWVSKKLHFEKDVDVNLFESTIRILGGLLSAYHLSGDSLFLRKAEDFGN
RLMPAFRTPSKIPYSDVNIGTGVAHPPRWTSDSTVAEVTSIQLEFRELSRLTGDKKFQEA
VEKVTQHIHGLSGKKDGLVPMFINTHSGLFTHLGVFTLGARADSYYEYLLKQWIQGGKQE
TQLLEDYVEAIEGVRTHLLRHSEPSKLTFVGELAHGRFSAKMDHLVCFLPGTLALGVYHG
LPASHMELAQELMETCYQMNRQMETGLSPEIVHFNLYPQPGRRDVEVKPADRHNLLRPET
VESLFYLYRVTGDRKYQDWGWEILQSFSRFTRVPSGGYSSINNVQDPQKPEPRDKMESFF
LGETLKYLFLLFSDDPNLLSLDAYVFNTEAHPLPIWTPA

Important features of the protein:
Transmembrane domain:
amino acids 21-40 and 84-105 (type II)

FIGURE 117

GTGGGATTTATTTGAGTGCAAGATCGTTTTCTCAGTGGTGGTGGAAGTTGCCTCATCGCA
GGCAGATGTTGGGGCTTTGTCCGAACAGCTCCCCTCTGCCAGCTTCTGTAGATAAGGGTT
AAAAACTAATATTTATATGACAGAAGAAAAAG**ATG**TCATTCCGTAAAGTAAACATCATCA
TCTTGGTCCTGGCTGTTGCTCTCTTCTTACTGGTTTTGCACCATAACTTCCTCAGCTTGA
GCAGTTTGTTAAGGAATGAGGTTACAGATTCAGGAATTGTAGGGCCTCAACCTATAGACT
TTGTCCCAAATGCTCTCCGACATGCAGTAGATGGGAGACAAGAGGAGATTCCTGTGGTCA
TCGCTGCATCTGAAGACAGGCTTGGGGGGGCCATTGCAGCTATAAACAGCATTCAGCACA
ACACTCGCTCCAATGTGATTTTCTACATTGTTACTCTCAACAATACAGCAGACCATCTCC
GGTCCTGGCTCAACAGTGATTCCCTGAAAAGCATCAGATACAAAATTGTCAATTTTGACC
CTAAACTTTTGGAAGGAAAAGTAAAGGAGGATCCTGACCAGGGGGAATCCATGAAACCTT
TAACCTTTGCAAGGTTCTACTTGCCAATTCTGGTTCCCAGCGCAAAGAAGGCCATATACA
TGGATGATGATGTAATTGTGCAAGGTGATATTCTTGCCCTTTACAATACAGCACTGAAGC
CAGGACATGCAGCTGCATTTTCAGAAGATTGTGATTCAGCCTCTACTAAAGTTGTCATCC
GTGGAGCAGGAAACCAGTACAATTACATTGGCTATCTTGACTATAAAAAGGAAAGAATTC
GTAAGCTTTCCATGAAAGCCAGCACTTGCTCATTTAATCCTGGAGTTTTTGTTGCAAACC
TGACGGAATGGAAACGACAGAATATAACTAACCAACTGGAAAAATGGATGAAACTCAATG
TAGAAGAGGGACTGTATAGCAGAACCCTGGCTGGTAGCATCACAACACCTCCTCTGCTTA
TCGTATTTTATCAACAGCACTCTACCATCGATCCTATGTGGAATGTCCGCCACCTTGGTT
CCAGTGCTGGAAAACGATATTCACCTCAGTTTGTAAAGGCTGCCAAGTTACTCCATTGGA
ATGGACATTTGAAGCCATGGGGAAGGACTGCTTCATATACTGATGTTTGGGAAAAATGGT
ATATTCCAGACCCAACAGGCAAATTCAACCTAATCCGAAGATATACCGAGATCTCAAACA
TAAAG**TGA**AACAGAATTTGAACTGTAAGCAAGCATTTCTCAGGAAGTCCTGGAAGATAGC
ATGCATGGGAAGTAACAGTTGCTAGGCTTCAATGCCTATCGGTAGCAAGCCATGGAAAAA
GATGTGTCAGCTAGGTAAAGATGACAAACTGCCCTGTCTGGCAGTCAGCTTCCCAGACAG
ACTATAGACTATAAATATGTCTCCATCTGCCTTACCAAGTGTTTTCTTACTACAATGCTG
AATGACTGGAAAGAAGAACTGATATGGCTAGTTCAGCTAGCTGGTACAGATAATTCAAAA
CTGCTGTTGGTTTTAATTTTGTAACCTGTGGCCTGATCTGTAAATAAAACTTACATTTTTC

FIGURE 118

MSFRKVNIIILVLAVALFLLVLHHNFLSLSSLLRNEVTDSGIVGPQPIDFVPNALRHAVD
GRQEEIPVVIAASEDRLGGAIAAINSIQHNTRSNVIFYIVTLNNTADHLRSWLNSDSLKS
IRYKIVNFDPKLLEGKVKEDPDQGESMKPLTFARFYLPILVPSAKKAIYMDDDVIVQGDI
LALYNTALKPGHAAAFSEDCDSASTKVVIRGAGNQYNYIGYLDYKKERIRKLSMKASTCS
FNPGVFVANLTEWKRQNITNQLEKWMKLNVEEGLYSRTLAGSITTPPLLIVFYQQHSTID
PMWNVRHLGSSAGKRYSPQFVKAAKLLHWNGHLKPWGRTASYTDVWEKWYIPDPTGKFNL
IRRYTEISNIK

FIGURE 119

CCATCCCTGAGATCTTTTTATAAAAAACCCAGTCTTTGCTGACCAGACAAAGCATACCAG
ATCTCACCAGAGAGTCGCAGACACT<u>**ATG**</u>CTGCCTCCCATGGCCCTGCCCAGTGTGTCCTG
GATGCTGCTTTCCTGCCTCATTCTCCTGTGTCAGGTTCAAGGTGAAGAAACCCAGAAGGA
ACTGCCCTCTCCACGGATCAGCTGTCCCAAAGGCTCCAAGGCCTATGGCTCCCCCTGCTA
TGCCTTGTTTTTGTCACCAAAATCCTGGATGGATGCAGATCTGGCTTGCCAGAAGCGGCC
CTCTGGAAAACTGGTGTCTGTGCTCAGTGGGGCTGAGGGATCCTTCGTGTCCTCCCTGGT
GAGGAGCATTAGTAACAGCTACTCATACATCTGGATTGGGCTCCATGACCCCACACAGGG
CTCTGAGCCTGATGGAGATGGATGGGAGTGGAGTAGCACTGATGTGATGAATTACTTTGC
ATGGGAGAAAAATCCCTCCACCATCTTAAACCCTGGCCACTGTGGGAGCCTGTCAAGAAG
CACAGGATTTCTGAAGTGGAAAGATTATAACTGTGATGCAAAGTTACCCTATGTCTGCAA
GTTCAAGGAC<u>**TAG**</u>GGCAGGTGGGAAGTCAGCAGCCTCAGCTTGGCGTGCAGCTCATCATG
GACATGAGACCAGTGTGAAGACTCACCCTGGAAGAGAATATTCTCCCCAAACTGCCCTAC
CTGACTACCTTGTCATGATCCTCCTTCTTTTTCCTTTTTCTTCACCTTCATTTCAGGCTT
TTCTCTGTCTTCCATGTCTTGAGATCTCAGAGAATAATAATAAAAATGTTACTTTATAAA
AAAAAAAAAAAAAAAAAA

FIGURE 120

MLPPMALPSVSWMLLSCLILLCQVQGEETQKELPSPRISCPKGSKAYGSPCYALFLSPKS
WMDADLACQKRPSGKLVSVLSGAEGSFVSSLVRSISNSYSYIWIGLHDPTQGSEPDGDGW
EWSSTDVMNYFAWEKNPSTILNPGHCGSLSRSTGFLKWKDYNCDAKLPYVCKFKD

Important features:
Signal peptide:
amino acids 1-26

C-type lectin domain signature:
amino acids 146-171

FIGURE 121

AAAGTTACATTTTCTCTGGAACTCTCCTAGGCCACTCCCTGCTGATGCAACATCTGGGTT
TGGGCAGAAAGGAGGGTGCTTCGGAGCCCGCCCTTTCTGAGCTTCCTGGGCCGGCTCTAG
AACAATTCAGGCTTCGCTGCGACTCAGACCTCAGCTCCAACATATGCATTCTGAAGAAAG
ATGGCTGAGATGGACAGAATGCTTTATTTTGGAAAGAAACAATGTTCTAGGTCAAACTGA
GTCTACCAAATGCAGACTTTCACAATGGTTCTAGAAGAAATCTGGACAAGTCTTTTCATG
TGGTTTTTCTACGCATTGATTCCATGTTTGCTCACAGATGAAGTGGCCATTCTGCCTGCC
CCTCAGAACCTCTCTGTACTCTCAACCAACATGAAGCATCTCTTGATGTGGAGCCCAGTG
ATCGCGCCTGGAGAAACAGTGTACTATTCTGTCGAATACCAGGGGGAGTACGAGAGCCTG
TACACGAGCCACATCTGGATCCCCAGCAGCTGGTGCTCACTCACTGAAGGTCCTGAGTGT
GATGTCACTGATGACATCACGGCCACTGTGCCATACAACCTTCGTGTCAGGGCCACATTG
GGCTCACAGACCTCAGCCTGGAGCATCCTGAAGCATCCCTTTAATAGAAACTCAACCATC
CTTACCCGACCTGGGATGGAGATCACCAAAGATGGCTTCCACCTGGTTATTGAGCTGGAG
GACCTGGGGCCCCAGTTTGAGTTCCTTGTGGCCTACTGGAGGAGGGAGCCTGGTGCCGAG
GAACATGTCAAAATGGTGAGGAGTGGGGGTATTCCAGTGCACCTAGAAACCATGGAGCCA
GGGGCTGCATACTGTGTGAAGGCCCAGACATTCGTGAAGGCCATTGGGAGGTACAGCGCC
TTCAGCCAGACAGAATGTGTGGAGGTGCAAGGAGAGGCCATTCCCCTGGTACTGGCCCTG
TTTGCCTTTGTTGGCTTCATGCTGATCCTTGTGGTCGTGCCACTGTTCGTCTGGAAAATG
GGCCGGCTGCTCCAGTACTCCTGTTGCCCCGTGGTGGTCCTCCCAGACACCTTGAAAATA
ACCAATTCACCCCAGAAGTTAATCAGCTGCAGAAGGGAGGAGGTGGATGCCTGTGCCACG
GCTGTGATGTCTCCTGAGGAACTCCTCAGGGCCTGGATCTCATAGGTTTGCGGAAGGGCC
CAGGTGAAGCCGAGAACCTGGTCTGCATGACATGGAAACCATGAGGGGACAAGTTGTGTT
TCTGTTTTCCGCCACGGACAAGGGATGAGAGAAGTAGGAAGAGCCTGTTGTCTACAAGTC
TAGAAGCAACCATCAGAGGCAGGGTGGTTTGTCTAACAGAACACTGACTGAGGCTTAGGG
GATGTGACCTCTAGACTGGGGGCTGCCACTTGCTGGCTGAGCAACCCTGGGAAAAGTGAC
TTCATCCCTTCGGTCCTAAGTTTTCTCATCTGTAATGGGGGAATTACCTACACACCTGCT
AAACACACACACACACAGAGTCTCTCTATATATACACACGTACACATAAATACACCCAGC
ACTTGCAAGGCTAGAGGGAAACTGGTGACACTCTACAGTCTGACTGATTCAGTGTTTCTG
GAGAGCAGGACATAAATGTATGATGAGAATGATCAAGGACTCTACACACTGGGTGGCTTG
GAGAGCCCACTTTCCCAGAATAATCCTTGAGAGAAAAGGAATCATGGGAGCAATGGTGTT
GAGTTCACTTCAAGCCCAATGCCGGTGCAGAGGGGAATGGCTTAGCGAGCTCTACAGTAG
GTGACCTGGAGGAAGGTCACAGCCACACTGAAAATGGGATGTGCATGAACACGGAGGATC
CATGAACTACTGTAAAGTGTTGACAGTGTGTGCACACTGCAGACAGCAGGTGAAATGTAT
GTGTGCAATGCGACGAGAATGCAGAAGTCAGTAACATGTGCATGTTTGTTGTGCTCCTTT
TTTCTGTTGGTAAAGTACAGAATTCAGCAAATAAAAAGGGCCACCCTGGCCAAAAGCGGT
AAAAAAAAAAAAAAA

FIGURE 122

MQTFTMVLEEIWTSLFMWFFYALIPCLLTDEVAILPAPQNLSVLSTNMKHLLMWSPVIAP
GETVYYSVEYQGEYESLYTSHIWIPSSWCSLTEGPECDVTDDITATVPYNLRVRATLGSQ
TSAWSILKHPFNRNSTILTRPGMEITKDGFHLVIELEDLGPQFEFLVAYWRREPGAEEHV
KMVRSGGIPVHLETMEPGAAYCVKAQTFVKAIGRYSAFSQTECVEVQGEAIPLVLALFAF
VGFMLILVVVPLFVWKMGRLLQYSCCPVVVLPDTLKITNSPQKLISCRREEVDACATAVM
SPEELLRAWIS

Important features:
Signal peptide:
amino acids 1-29

Transmembrane domain:
amino acids 230-255

N-glycosylation sites:
amino acids 40-43 and 134-137

Tissue factor proteins homology:
amino acids 92-119

Integrins alpha chain protein homology:
amino acids 232-262

FIGURE 123

CGGACGCGTGGGCCGCCACCTCCGGAACAAGCC**ATG**GTGGCGGCGACGGTGGCAGCGGCG
TGGCTGCTCCTGTGGGCTGCGGCCTGCGCGCAGCAGGAGCAGGACTTCTACGACTTCAAG
GCGGTCAACATCCGGGGCAAACTGGTGTCGCTGGAGAAGTACCGCGGATCGGTGTCCCTG
GTGGTGAATGTGGCCAGCGAGTGCGGCTTCACAGACCAGCACTACCGAGCCCTGCAGCAG
CTGCAGCGAGACCTGGGCCCCCACCACTTTAACGTGCTCGCCTTCCCCTGCAACCAGTTT
GGCCAACAGGAGCCTGACAGCAACAAGGAGATTGAGAGCTTTGCCCGCCGCACCTACAGT
GTCTCATTCCCCATGTTTAGCAAGATTGCAGTCACCGGTACTGGTGCCCATCCTGCCTTC
AAGTACCTGGCCCAGACTTCTGGGAAGGAGCCCACCTGGAACTTCTGGAAGTACCTAGTA
GCCCCAGATGGAAAGGTGGTAGGGGCTTGGGACCCAACTGTGTCAGTGGAGGAGGTCAGA
CCCCAGATCACAGCGCTCGTGAGGAAGCTCATCCTACTGAAGCGAGAAGACTTA**TAA**CCA
CCGCGTCTCCTCCTCCACCACCTCATCCCGCCCACCTGTGTGGGGCTGACCAATGCAAAC
TCAAATGGTGCTTCAAAGGGAGAGACCCACTGACTCTCCTTCCTTTACTCTTATGCCATT
GGTCCCATCATTCTTGTGGGGGAAAAATTCTAGTATTTTGATTATTTGAATCTTACAGCA
ACAAATAGGAACTCCTGGCCAATGAGAGCTCTTGACCAGTGAATCACCAGCCGATACGAA
CGTCTTGCCAACAAAAATGTGTGGCAAATAGAAGTATATCAAGCAATAATCTCCCACCCA
AGGCTTCTGTAAACTGGGACCAATGATTACCTCATAGGGCTGTTGTGAGGATTAGGATGA
AATACCTGTGAAAGTGCCTAGGCAGTGCCAGCCAAATAGGAGGCATTCAATGAACATTTT
TTGCATATAAACCAAAAAATAACTTGTTATCAATAAAAACTTGCATCCAACATGAATTTC
CAGCCGATGATAATCCAGGCCAAAGGTTTAGTTGTTGTTATTTCCTCTGTATTATTTTCT
TCATTACAAAAGAAATGCAAGTTCATTGTAACAATCCAAACAATACCTCACGATATAAAA
TAAAAATGAAAGTATCCTCCTCAAAAA

FIGURE 124

MVAATVAAAWLLLWAAACAQQEQDFYDFKAVNIRGKLVSLEKYRGSVSLVVNVASECGFT
DQHYRALQQLQRDLGPHHFNVLAFPCNQFGQQEPDSNKEIESFARRTYSVSFPMFSKIAV
TGTGAHPAFKYLAQTSGKEPTWNFWKYLVAPDGKVVGAWDPTVSVEEVRPQITALVRKLI
LLKREDL

FIGURE 125

CGGACGCGTGGGCGGACGCGTGGGCGGACGCGTGGGTTGGGAGGGGGCAGGATGGGAGGG
AAAGTGAAGAAAACAGAAAAGGAGAGGGACAGAGGCCAGAGGACTTCTCATACTGGACAG
AAACCGATCAGGC<u>ATG</u>GAACTCCCCTTCGTCACTCACCTGTTCTTGCCCCTGGTGTTCCT
GACAGGTCTCTGCTCCCCCTTTAACCTGGATGAACATCACCCACGCCTATTCCCAGGGCC
ACCAGAAGCTGAATTTGGATACAGTGTCTTACAACATGTTGGGGGTGGACAGCGATGGAT
GCTGGTGGGCGCCCCCTGGGATGGGCCTTCAGGCGACCGGAGGGGGGACGTTTATCGCTG
CCCTGTAGGGGGGGCCCACAATGCCCCATGTGCCAAGGGCCACTTAGGTGACTACCAACT
GGGAAATTCATCTCATCCTGCTGTGAATATGCACCTGGGGATGTCTCTGTTAGAGACAGA
TGGTGATGGGGGATTCATGGTGAGC<u>TAA</u>GGAGAGGGTGGTGGCAGTGTCTCTGAAGGTCC
ATAAAAGAAAAAAGAGAAGTGTGGTAAGGGAAAATGGTCTGTGTGGAGGGGTCAAGGAGT
TAAAAACCCTAGAAAGCAAAAGGTAGGTAATGTCAGGGAGTAGTCTTCATGCCTCCTTCA
ACTGGGAGCATGTTCTGAGGGTGCCCTCCCAAGCCTGGGAGTAACTATTTCCCCCATCCC
CAGGCCTGTGCCCCTCTCTGGTCTCGTGCTTGTGGCAGCTCTGTCTTCAGTTCTGGGATA
TGTGCCCGTGTGGATGCTTCATTCCAGCCTCAGGGAAGCCTGGCACCCACTGCCCAACGT
GAGCCAGAGGAAGGCTGAGTACTTGGTTCCCAGAAGGAGATACTGGGTGGGAAAAAGATG
GGGCAAAGCGGTATGATGCCTGGCAAAGGGCCTGCATGGCTATCCTCATTGCTACCTAAT
GTGCTTGCAAAAGCTCCATGTTTCCTAACAGATTCAGACTCCTGGCCAGGTGTGGTGGCC
CACACCTGTAATTCTAGCACTTTGGGAGGCCAAGGTGGGCAGATCACTTGAGGTCAGGAG
TTCAAGACCAGCCTGGCCAACATGGTGAAACTCCATCTCTACTAAAAAAAAAAAAAATACA
AAAATTAGCTGGGTGCGCTAGTGCATGCCTGTAATCTCATCTACTCGGGAGGCTAAGACA
GGAGACTCTCACTTCAACCCAGGAGGTGGAGGTTGCGGTGAGCCAAGATTGTGCCTCTGC
ACTCTAGCGTGGGTGACAGAGTAAGCGAGACTCCATCTCAAAAATAATAATAATAATAAT
TCAGACTCCTTATCAGGAGTCCATGATCTGGCCTGGCACAGTAACTCATGCCTGTAATCC
CAACATTTTGGGAGGCCAACGCAGGAGGATTGCTTGAGGTCTGGAGGTTTGAGACCAGCC
TGGGCAACATAGAAAGACCCCATCTCTAAATAAATGTTTTAAAAAT

FIGURE 126

MELPFVTHLFLPLVFLTGLCSPFNLDEHHPRLFPGPPEAEFGYSVLQHVGGGQRWMLVGA
PWDGPSGDRRGDVYRCPVGGAHNAPCAKGHLGDYQLGNSSHPAVNMHLGMSLLETDGDGG
FMVS

Important features:
Signal peptide:
amino acids 1-22

Cell attachment sequence:
amino acids 70-73

N-glycosylation site:
amino acids 98-101

Integrins alpha chain proteins:
amino acids 67-81

FIGURE 127

GAGAGGACGAGGTGCCGCTGCCTGGAGAATCCTCCGCTGCCGTCGGCTCCCGGAGCCCAG
CCCTTTCCTAACCCAACCCAACCTAGCCCAGTCCCAGCCGCCAGCGCCTGTCCCTGTCAC
GGACCCCAGCGTTACC**ATG**CATCCTGCCGTCTTCCTATCCTTACCCGACCTCAGATGCTC
CCTTCTGCTCCTGGTAACTTGGGTTTTTACTCCTGTAACAACTGAAATAACAAGTCTTGC
TACAGAGAATATAGATGAAATTTTAAACAATGCTGATGTTGCTTTAGTAAATTTTTATGC
TGACTGGTGTCGTTTCAGTCAGATGTTGCATCCAATTTTTGAGGAAGCTTCCGATGTCAT
TAAGGAAGAATTTCCAAATGAAAATCAAGTAGTGTTTGCCAGAGTTGATTGTGATCAGCA
CTCTGACATAGCCCAGAGATACAGGATAAGCAAATACCCAACCCTCAAATTGTTTCGTAA
TGGGATGATGATGAAGAGAGAATACAGGGGTCAGCGATCAGTGAAAGCATTGGCAGATTA
CATCAGGCAACAAAAAAGTGACCCCATTCAAGAAATTCGGGACTTAGCAGAAATCACCAC
TCTTGATCGCAGCAAAAGAAATATCATTGGATATTTTGAGCAAAAGGACTCGGACAACTA
TAGAGTTTTTGAACGAGTAGCGAATATTTTGCATGATGACTGTGCCTTTCTTTCTGCATT
TGGGGATGTTTCAAAACCGGAAAGATATAGTGGCGACAACATAATCTACAAACCACCAGG
GCATTCTGCTCCGGATATGGTGTACTTGGGAGCTATGACAAATTTTGATGTGACTTACAA
TTGGATTCAAGATAAATGTGTTCCTCTTGTCCGAGAAATAACATTTGAAAATGGAGAGGA
ATTGACAGAAGAAGGACTGCCTTTTCTCATACTCTTTCACATGAAAGAAGATACAGAAAG
TTTAGAAATATTCCAGAATGAAGTAGCTCGGCAATTAATAAGTGAAAAAGGTACAATAAA
CTTTTTACATGCCGATTGTGACAAATTTAGACATCCTCTTCTGCACATACAGAAAACTCC
AGCAGATTGTCCTGTAATCGCTATTGACAGCTTTAGGCATATGTATGTGTTTGGAGACTT
CAAAGATGTATTAATTCCTGGAAAACTCAAGCAATTCGTATTTGACTTACATTCTGGAAA
ACTGCACAGAGAATTCCATCATGGACCTGACCCAACTGATACAGCCCCAGGAGAGCAAGC
CCAAGATGTAGCAAGCAGTCCACCTGAGAGCTCCTTCCAGAAACTAGCACCCAGTGAATA
TAGGTATACTCTATTGAGGGATCGAGATGAGCTT**TAA**AAACTTGAAAAACAGTTTGTAAG
CCTTTCAACAGCAGCATCAACCTACGTGGTGGAAATAGTAAACCTATATTTTCATAATTC
TATGTGTATTTTTATTTTGAATAAACAGAAAGAAATTTAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAA

FIGURE 128

MHPAVFLSLPDLRCSLLLLVTWVFTPVTTEITSLATENIDEILNNADVALVNFYADWCRF
SQMLHPIFEEASDVIKEEFPNENQVVFARVDCDQHSDIAQRYRISKYPTLKLFRNGMMMK
REYRGQRSVKALADYIRQQKSDPIQEIRDLAEITTLDRSKRNIIGYFEQKDSDNYRVFER
VANILHDDCAFLSAFGDVSKPERYSGDNIIYKPPGHSAPDMVYLGAMTNFDVTYNWIQDK
CVPLVREITFENGEELTEEGLPFLILFHMKEDTESLEIFQNEVARQLISEKGTINFLHAD
CDKFRHPLLHIQKTPADCPVIAIDSFRHMYVFGDFKDVLIPGKLKQFVFDLHSGKLHREF
HHGPDPTDTAPGEQAQDVASSPPESSFQKLAPSEYRYTLLRDRDEL

Important features:
Signal peptide:
amino acids 1-29

Endoplasmic reticulum targeting sequence:
amino acids 403-406

Tyrosine kinase phosphorylation site:
amino acids 203-211

Thioredoxin family proteins:
amino acids 50-66

FIGURE 129

GAGCAGGACGGAGCC<u>ATG</u>GACCCCGCCAGGAAAGCAGGTGCCCAGGCCATGATCTGGACT
GCAGGCTGGCTGCTGCTGCTGCTGCTTCGCGGAGGAGCGCAGGCCCTGGAGTGCTACAGC
TGCGTGCAGAAAGCAGATGACGGATGCTCCCCGAACAAGATGAAGACAGTGAAGTGCGCG
CCGGGCGTGGACGTCTGCACCGAGGCCGTGGGGGCGGTGGAGACCATCCACGGACAATTC
TCGCTGGCAGTGCGGGGTTGCGGTTCGGGACTCCCCGGCAAGAATGACCGCGGCCTGGAT
CTTCACGGGCTTCTGGCGTTCATCCAGCTGCAGCAATGCGCTCAGGATCGCTGCAACGCC
AAGCTCAACCTCACCTCGCGGGCGCTCGACCCGGCAGGTAATGAGAGTGCATACCCGCCC
AACGGCGTGGAGTGCTACAGCTGTGTGGGCCTGAGCCGGGAGGCGTGCCAGGGTACATCG
CCGCCGGTCGTGAGCTGCTACAACGCCAGCGATCATGTCTACAAGGGCTGCTTCGACGGC
AACGTCACCTTGACGGCAGCTAATGTGACTGTGTCCTTGCCTGTCCGGGGCTGTGTCCAG
GATGAATTCTGCACTCGGGATGGAGTAACAGGCCCAGGGTTCACGCTCAGTGGCTCCTGT
TGCCAGGGGTCCCGCTGTAACTCTGACCTCCGCAACAAGACCTACTTCTCCCCTCGAATC
CCACCCCTTGTCCGGCTGCCCCCTCCAGAGCCCACGACTGTGGCCTCAACCACATCTGTC
ACCACTTCTACCTCGGCCCCAGTGAGACCCACATCCACCACCAAACCCATGCCAGCGCCA
ACCAGTCAGACTCCGAGACAGGGAGTAGAACACGAGGCCTCCCGGGATGAGGAGCCCAGG
TTGACTGGAGGCGCCGCTGGCCACCAGGACCGCAGCAATTCAGGGCAGTATCCTGCAAAA
GGGGGGCCCCAGCAGCCCCATAATAAAGGCTGTGTGGCTCCCACAGCTGGATTGGCAGCC
CTTCTGTTGGCCGTGGCTGCTGGTGTCCTACTG<u>TGA</u>GCTTCTCCACCTGGAAATTTCCCT
CTCACCTACTTCTCTGGCCCTGGGTACCCCTCTTCTCATCACTTCCTGTTCCCACCACTG
GACTGGGCTGGCCCAGCCCCTGTTTTTCCAACATTCCCCAGTATCCCCAGCTTCTGCTGC
GCTGGTTTGCGGCTTTGGGAAATAAAATACCGTTGTATATATTCTGCCAGGGGTGTTCTA
GCTTTTTGAGGACAGCTCCTGTATCCTTCTCATCCTTGTCTCTCCGCTTGTCCTCTTGTG
ATGTTAGGACAGAGTGAGAGAAGTCAGCTGTCACGGGGAAGGTGAGAGAGAGGATGCTAA
GCTTCCTACTCACTTTCTCCTAGCCAGCCTGGACTTTGGAGCGTGGGGTGGGTGGACAA
TGGCTCCCCACTCTAAGCACTGCCTCCCCTACTCCCCGCATCTTTGGGAATCGGTTCCC
CATATGTCTTCCTTACTAGACTGTGAGCTCCTCGAGGGGGGGCCCGGTACCCAATTCGCC
CTATAGTGAGTCGTA

FIGURE 130

MDPARKAGAQAMIWTAGWLLLLLLRGGAQALECYSCVQKADDGCSPNKMKTVKCAPGVDV
CTEAVGAVETIHGQFSLAVRGCGSGLPGKNDRGLDLHGLLAFIQLQQCAQDRCNAKLNLT
SRALDPAGNESAYPPNGVECYSCVGLSREACQGTSPPVVSCYNASDHVYKGCFDGNVTLT
AANVTVSLPVRGCVQDEFCTRDGVTGPGFTLSGSCCQGSRCNSDLRNKTYFSPRIPPLVR
LPPPEPTTVASTTSVTTSTSAPVRPTSTTKPMPAPTSQTPRQGVEHEASRDEEPRLTGGA
AGHQDRSNSGQYPAKGGPQQPHNKGCVAPTAGLAALLLAVAAGVLL

FIGURE 131

AAACTTGACGCC**ATG**AAGATCCCGGTCCTTCCTGCCGTGGTGCTCCTCTCCCTCCTGGTG
CTCCACTCTGCCCAGGGAGCCACCCTGGGTGGTCCTGAGGAAGAAAGCACCATTGAGAAT
TATGCGTCACGACCCGAGGCCTTTAACACCCCGTTCCTGAACATCGACAAATTGCGATCT
GCGTTTAAGGCTGATGAGTTCCTGAACTGGCACGCCCTCTTTGAGTCTATCAAAAGGAAA
CTTCCTTTCCTCAACTGGGATGCCTTTCCTAAGCTGAAAGGACTGAGGAGCGCAACTCCT
GATGCCCAG**TGA**CCATGACCTCCACTGGAAGAGGGGGCTAGCGTGAGCGCTGATTCTCAA
CCTACCATAACTCTTTCCTGCCTCAGGAACTCCAATAAAACATTTTCCATCCAAA

FIGURE 132

MKIPVLPAVVLLSLLVLHSAQGATLGGPEEESTIENYASRPEAFNTPFLNIDKLRSAFKA
DEFLNWHALFESIKRKLPFLNWDAFPKLKGLRSATPDAQ

FIGURE 133

CAGTTCTGAAATCAATGGAGTTAATTTAGGGAATACAAACCAGCC**ATG**GGGGTGGAGATT
GCCTTTGCCTCAGTGATTCTCACCTGCCTCTCCCTTCTGGCAGCAGGAGTCTCCCAGGTT
GTTCTTCTCCAGCCAGTTCCAACTCAGGAGACAGGTCCCAAGGCCATGGGAGATCTCTCC
TGTGGCTTTGCCGGCCACTCA**TGA**GAGTGTTTTTGTGTAAAGTATTTTTTAGAATACTGT
TGACTTCTTCATGATTTAATAACCATCCTTTGCGAAGTTTTATGAGGCTTTAGGGGAATG
TCAACCCTCAAATTTTTGTTATACTAGATGGCTTCCATTTACCCACCACTATTTTAAGGT
CCCTTTATTTTTAGGTTCAAGGTTCATTTGACTTGAGAAAGTGCCCTTCTGCAGCTTCAT
TGATTTTGTTTATCTTCACTATTAATTGTAACGATTAAAAAAGAATAAGAGCACGCAGAC
CTCTAGGAGAATATTTTATCCCTGGGTGCCCCTGACACATTTATGTAGTGATCCCACAAA
TGTGATTGTTAATTTAAATGTTATTCTAATATTAGTACATTCAGTTGTGATGTAATATGA
ATAACCAGAATCTATTTCTTAAAAGTTTTGAGTATATTTTTCAACTAGATATTTGTATAG
AAAGACTGAATAGTGATG

FIGURE 134

MGVEIAFASVILTCLSLLAAGVSQVVLLQPVPTQETGPKAMGDLSCGFAGHS

FIGURE 135

GGGGAATCTGCAGTAGGTCTGCCGGCG**ATG**GAGTGGTGGGCTAGCTCGCCGCTTCGGCTC
TGGCTGCTGTTGTTCCTCCTGCCCTCAGCGCAGGGCCGCCAGAAGGAGTCAGGTTCAAAA
TGGAAAGTATTTATTGACCAAATTAACAGGTCTTTGGAGAATTACGAACCATGTTCAAGT
CAAAACTGCAGCTGCTACCATGGTGTCATAGAAGAGGATCTAACTCCTTTCCGAGGAGGC
ATCTCCAGGAAGATGATGGCAGAGGTAGTCAGACGGAAGCTAGGGACCCACTATCAGATC
ACTAAGAACAGACTGTACCGGGAAAATGACTGCATGTTCCCCTCAAGGTGTAGTGGTGTT
GAGCACTTTATTTTGGAAGTGATCGGGCGTCTCCCTGACATGGAGATGGTGATCAATGTA
CGAGATTATCCTCAGGTTCCTAAATGGATGGAGCCTGCCATCCCAGTCTTCTCCTTCAGT
AAGACATCAGAGTACCATGATATCATGTATCCTGCTTGGACATTTTGGGAAGGGGGACCT
GCTGTTTGGCCAATTTATCCTACAGGTCTTGGACGGTGGGACCTCTTCAGAGAAGATCTG
GTAAGGTCAGCAGCACAGTGGCCATGGAAAAAGAAAAACTCTACAGCATATTTCCGAGGA
TCAAGGACAAGTCCAGAACGAGATCCTCTCATTCTTCTGTCTCGGAAAAACCCAAAACTT
GTTGATGCAGAATACACCAAAAACCAGGCCTGGAAATCTATGAAAGATACCTTAGGAAAG
CCAGCTGCTAAGGATGTCCATCTTGTGGATCACTGCAAATACAAGTATCTGTTTAATTTT
CGAGGCGTAGCTGCAAGTTTCCGGTTTAAACACCTCTTCCTGTGTGGCTCACTTGTTTTC
CATGTTGGTGATGAGTGGCTAGAATTCTTCTATCCACAGCTGAAGCCATGGGTTCACTAT
ATCCCAGTCAAAACAGATCTCTCCAATGTCCAAGAGCTGTTACAATTTGTAAAAGCAAAT
GATGATGTAGCTCAAGAGATTGCTGAAAGGGGAAGCCAGTTTATTAGGAACCATTTGCAG
ATGGATGACATCACCTGTTACTGGGAGAACCTCTTGAGTGAATACTCTAAATTCCTGTCT
TATAATGTAACGAGAAGGAAAGGTTATGATCAAATTATTCCCAAAATGTTGAAAACTGAA
CTA**TAG**TAGTCATCATAGGACCATAGTCCTCTTTGTGGCAACAGATCTCAGATATCCTAC
GGTGAGAAGCTTACCATAAGCTTGGCTCCTATACCTTGAATATCTGCTATCAAGCCAAAT
ACCTGGTTTTCCTTATCATGCTGCACCCAGAGCAACTCTTGAGAAAGATTTAAAATGTGT
CTAATACACTGATATGAAGCAGTTCAACTTTTTGGATGAATAAGGACCAGAAATCGTGAG
ATGTGGATTTTGAACCCAACTCTACCTTTCATTTTCTTAAGACCAATCACAGCTTGTGCC
TCAGATCATCCACCTGTGTGAGTCCATCACTGTGAAATTGACTGTGTCCATGTGATGATG
CCCTTTGTCCCATTATTTGGAGCAGAAAATTCGTCATTTGGAAGTAGTACAACTCATTGC
TGGAATTGTGAAATTATTCAAGGCGTGATCTCTGTCACTTTATTTTAATGTAGGAAACCC
TATGGGGTTTATGAAAAATACTTGGGGATCATTCTCTGAATGGTCTAAGGAAGCGGTAGC
CATGCCATGCAATGATGTAGGAGTTCTCTTTTGTAAAACCATAAACTCTGTTACTCAGGA
GGTTTCTATAATGCCACATAGAAAGAGGCCAATTGCATGAGTAATTATTGCAATTGGATT
TCAGGTTCCCTTTTTGTGCCTTCATGCCCTACTTCTTAATGCCTCTCTAAAGCCAAA

FIGURE 136

MEWWASSPLRLWLLLFLLPSAQGRQKESGSKWKVFIDQINRSLENYEPCSSQNCSCYHGV
IEEDLTPFRGGISRKMMAEVVRRKLGTHYQITKNRLYRENDCMFPSRCSGVEHFILEVIG
RLPDMEMVINVRDYPQVPKWMEPAIPVFSFSKTSEYHDIMYPAWTFWEGGPAVWPIYPTG
LGRWDLFREDLVRSAAQWPWKKKNSTAYFRGSRTSPERDPLILLSRKNPKLVDAEYTKNQ
AWKSMKDTLGKPAAKDVHLVDHCKYKYLFNFRGVAASFRFKHLFLCGSLVFHVGDEWLEF
FYPQLKPWVHYIPVKTDLSNVQELLQFVKANDDVAQEIAERGSQFIRNHLQMDDITCYWE
NLLSEYSKFLSYNVTRRKGYDQIIPKMLKTEL

FIGURE 137

ATTCTCCTAGAGCATCTTTGGAAGC**ATG**AGGCCACGATGCTGCATCTTGGCTCTTGTCTG
CTGGATAACAGTCTTCCTCCTCCAGTGTTCAAAAGGAACTACAGACGCTCCTGTTGGCTC
AGGACTGTGGCTGTGCCAGCCGACACCCAGGTGTGGGAACAAGATCTACAACCCTTCAGA
GCAGTGCTGTTATGATGATGCCATCTTATCCTTAAAGGAGACCCGCCGCTGTGGCTCCAC
CTGCACCTTCTGGCCCTGCTTTGAGCTCTGCTGTCCCGAGTCTTTTGGCCCCCAGCAGAA
GTTTCTTGTGAAGTTGAGGGTTCTGGGTATGAAGTCTCAGTGTCACTTATCTCCCATCTC
CCGGAGCTGTACCAGGAACAGGAGGCACGTCCTGTACCCA**TAA**AAACCCCAGGCTCCACT
GGCAGACGGCAGACAAGGGGAGAAGAGACGAAGCAGCTGGACATCGGAGACTACAGTTGA
ACTTCGGAGAGAAGCAACTTGACTTCAGAGGGATGGCTCAATGACATAGCTTTGGAGAGG
AGCCCAGCTGGGGATGGCCAGACTTCAGGGGAAGAATGCCTTCCTGCTTCATCCCCTTTC
CAGCTCCCCTTCCCGCTGAGAGCCACTTTCATCGGCAATAAAATCCCCCACATTTACCATCT

FIGURE 138

MRPRCCILALVCWITVFLLQCSKGTTDAPVGSGLWLCQPTPRCGNKIYNPSEQCCYDDAI
LSLKETRRCGSTCTFWPCFELCCPESFGPQQKFLVKLRVLGMKSQCHLSPISRSCTRNRR
HVLYP

Important features:
Signal sequence:
amino acids 1-21

N-myristoylation sites:
amino acids 33-39, 70-76

FIGURE 139

CCTCTGTCCACTGCTTTCGTGAAGACAAG**ATG**AAGTTCACAATTGTCTTTGCTGGACTTC
TTGGAGTCTTTCTAGCTCCTGCCCTAGCTAACTATAATATCAACGTCAATGATGACAACA
ACAATGCTGGAAGTGGGCAGCAGTCAGTGAGTGTCAACAATGAACACAATGTGGCCAATG
TTGACAATAACAACGGATGGGACTCCTGGAATTCCATCTGGGATTATGGAAATGGCTTTG
CTGCAACCAGACTCTTTCAAAAGAAGACATGCATTGTGCACAAAATGAACAAGGAAGTCA
TGCCCTCCATTCAATCCCTTGATGCACTGGTCAAGGAAAAGAAGCTTCAGGGTAAGGGAC
CAGGAGGACCACCTCCCAAGGGCCTGATGTACTCAGTCAACCCAAACAAAGTCGATGACC
TGAGCAAGTTCGGAAAAAACATTGCAAACATGTGTCGTGGGATTCCAACATACATGGCTG
AGGAGATGCAAGAGGCAAGCCTGTTTTTTTACTCAGGAACGTGCTACACGACCAGTGTAC
TATGGATTGTGGACATTTCCTTCTGTGGAGACACGGTGGAGAAC**TAA**ACAATTTTTTAAA
GCCACTATGGATTTAGTCATCTGAATATGCTGTGCAGAAAAAATATGGGCTCCAGTGGTT
TTTACCATGTCATTCTGAAATTTTTCTCTACTAGTTATGTTTGATTTCTTTAAGTTTCAA
TAAAATCATTTAGCATTGAAAAAAA

FIGURE 140

MKFTIVFAGLLGVFLAPALANYNINVNDDNNNAGSGQQSVSVNNEHNVANVDNNNGWDSW
NSIWDYGNGFAATRLFQKKTCIVHKMNKEVMPSIQSLDALVKEKKLQGKGPGGPPPKGLM
YSVNPNKVDDLSKFGKNIANMCRGIPTYMAEEMQEASLFFYSGTCYTTSVLWIVDISFCG
DTVEN

Signal Peptide:
amino acids 1-20

N-myristoylation Sites:
amino acids 67-72, 118-123, 163-168

Flavodoxin protein homology:
amino acids 156-174

FIGURE 141

GGTCCTTAATGGCAGCAGCCGCCGCTACCAAGATCCTTCTGTGCCTCCCGCTTCTGCTCC
TGCTGTCCGGCTGGTCCCGGGCTGGGCGAGCCGACCCTCACTCTCTTTGCTATGACATCA
CCGTCATCCCTAAGTTCAGACCTGGACCACGGTGGTGTGCGGTTCAAGGCCAGGTGGATG
AAAAGACTTTTCTTCACTATGACTGTGGCAACAAGACAGTCACACCTGTCAGTCCCCTGG
GGAAGAAACTAAATGTCACAACGGCCTGGAAAGCACAGAACCCAGTACTGAGAGAGGTGG
TGGACATACTTACAGAGCAACTGCGTGACATTCAGCTGGAGAATTACACACCCAAGGAAC
CCCTCACCCTGCAGGCAAGGATGTCTTGTGAGCAGAAAGCTGAAGGACACAGCAGTGGAT
CTTGGCAGTTCAGTTTCGATGGGCAGATCTTCCTCCTCTTTGACTCAGAGAAGAGAATGT
GGACAACGGTTCATCCTGGAGCCAGAAAGATGAAAGAAAAGTGGGAGAATGACAAGGTTG
TGGCCATGTCCTTCCATTACTTCTCAATGGGAGACTGTATAGGATGGCTTGAGGACTTCT
TGATGGGCATGGACAGCACCCTGGAGCCAAGTGCAGGAGCACCACTCGCCATGTCCTCAG
GCACAACCCAACTCAGGGCCACAGCCACCACCCTCATCCTTTGCTGCCTCCTCATCATCC
TCCCCTGCTTCATCCTCCCTGGCATCTGAGGAGAGTCCTTTAGAGTGACAGGTTAAAGCT
GATACCAAAAGGCTCCTGTGAGCACGGTCTTGATCAAACTCGCCCTTCTGTCTGGCCAGC
TGCCCACGACCTACGGTGTATGTCCAGTGGCCTCCAGCAGATCATGATGACATCATGGAC
CCAATAGCTCATTCACTGCCTTGATTCCTTTTGCCAACAATTTTACCAGCAGTTATACCT
AACATATTATGCAATTTTCTCTTGGTGCTACCTGATGGAATTCCTGCACTTAAAGTTCTG
GCTGACTAAACAAGATATATCATTTTCTTTCTTCTCTTTTTGTTTGGAAAATCAAGTACT
TCTTTGAATGATGATCTCTTTCTTGCAAATGATATTGTCAGTAAAATAATCACGTTAGAC
TTCAGACCTCTGGGGATTCTTTCCGTGTCCTGAAAGAGAATTTTTAAATTATTTAATAAG
AAAAAATTTATATTAATGATTGTTTCCTTTAGTAATTTATTGTTCTGTACTGATATTTAA
ATAAAGAGTTCTATTTCCCAAAAAAAAAAAAAAAAAA

FIGURE 142

MAAAAATKILLCLPLLLLLSGWSRAGRADPHSLCYDITVIPKFRPGPRWCAVQGQVDEKT
FLHYDCGNKTVTPVSPLGKKLNVTTAWKAQNPVLREVVDILTEQLRDIQLENYTPKEPLT
LQARMSCEQKAEGHSSGSWQFSFDGQIFLLFDSEKRMWTTVHPGARKMKEKWENDKVVAM
SFHYFSMGDCIGWLEDFLMGMDSTLEPSAGAPLAMSSGTTQLRATATTLILCCLLIILPC
FILPGI

Important features:
Signal peptide:
amino acids 1-25

Transmembrane domain:
amino acids 224-246

N-glycosylation site:
amino acids 68-72, 82-86

N-myristoylation site:
amino acids 200-206, 210-216

Amidation site:
amino acids 77-81

FIGURE 143

AATGTGAGAGGGGCTGATGGAAGCTGATAGGCAGGACTGGAGTGTTAGCACCAGTACTGG
ATGTGACAGCAGGCAGAGGAGCACTTAGCAGCTTATTCAGTGTCCGATTCTGATTCCGGC
AAGGATCCAAGC**ATG**GAATGCTGCCGTCGGGCAACTCCTGGCACACTGCTCCTCTTTCTG
GCTTTCCTGCTCCTGAGTTCCAGGACCGCACGCTCCGAGGAGGACCGGGACGGCCTATGG
GATGCCTGGGGCCCATGGAGTGAATGCTCACGCACCTGCGGGGGAGGGGCCTCCTACTCT
CTGAGGCGCTGCCTGAGCAGCAAGAGCTGTGAAGGAAGAAATATCCGATACAGAACATGC
AGTAATGTGGACTGCCCACCAGAAGCAGGTGATTTCCGAGCTCAGCAATGCTCAGCTCAT
AATGATGTCAAGCACCATGGCCAGTTTTATGAATGGCTTCCTGTGTCTAATGACCCTGAC
AACCCATGTTCACTCAAGTGCCAAGCCAAAGGAACAACCCTGGTTGTTGAACTAGCACCT
AAGGTCTTAGATGGTACGCGTTGCTATACAGAATCTTTGGATATGTGCATCAGTGGTTTA
TGCCAAATTGTTGGCTGCGATCACCAGCTGGGAAGCACCGTCAAGGAAGATAACTGTGGG
GTCTGCAACGGAGATGGGTCCACCTGCCGGCTGGTCCGAGGGCAGTATAAATCCCAGCTC
TCCGCAACCAAATCGGATGATACTGTGGTTGCACTTCCCTATGGAAGTAGACATATTCGC
CTTGTCTTAAAAGGTCCTGATCACTTATATCTGGAAACCAAAACCCTCCAGGGGACTAAA
GGTGAAAACAGTCTCAGCTCCACAGGAACTTTCCTTGTGGACAATTCTAGTGTGGACTTC
CAGAAATTTCCAGACAAAGAGATACTGAGAATGGCTGGACCACTCACAGCAGATTTCATT
GTCAAGATTCGTAACTCGGGCTCCGCTGACAGTACAGTCCAGTTCATCTTCTATCAACCC
ATCATCCACCGATGGAGGGAGACGGATTTCTTTCCTTGCTCAGCAACCTGTGGAGGAGGT
TATCAGCTGACATCGGCTGAGTGCTACGATCTGAGGAGCAACCGTGTGGTTGCTGACCAA
TACTGTCACTATTACCCAGAGAACATCAAACCCAAACCCAAGCTTCAGGAGTGCAACTTG
GATCCTTGTCCAGCCAGTGACGGATACAAGCAGATCATGCCTTATGACCTCTACCATCCC
CTTCCTCGGTGGGAGGCCACCCCATGGACCGCGTGCTCCTCCTCGTGTGGGGGGGGCATC
CAGAGCCGGGCAGTTTCCTGTGTGGAGGAGGACATCCAGGGGCATGTCACTTCAGTGGAA
GAGTGGAAATGCATGTACACCCCTAAGATGCCCATCGCGCAGCCCTGCAACATTTTTGAC
TGCCCTAAATGGCTGGCACAGGAGTGGTCTCCGTGCACAGTGACATGTGGCCAGGGCCTC
AGATACCGTGTGGTCCTCTGCATCGACCATCGAGGAATGCACACAGGAGGCTGTAGCCCA
AAAACAAAGCCCCACATAAAAGAGGAATGCATCGTACCCACTCCCTGCTATAAACCCAAA
GAGAAACTTCCAGTCGAGGCCAAGTTGCCATGGTTCAAACAAGCTCAAGAGCTAGAAGAA
GGAGCTGCTGTGTCAGAGGAGCCCTCG**TAA**GTTGTAAAAGCACAGACTGTTCTATATTTG
AAACTGTTTTGTTTAAAGAAAGCAGTGTCTCACTGGTTGTAGCTTTCATGGGTTCTGAAC
TAAGTGTAATCATCTCACCAAAGCTTTTTGGCTCTCAAATTAAAGATTGATTAGTTTCAA
AAAAAAAAA

FIGURE 144

MECCRRATPGTLLLFLAFLLLSSRTARSEEDRDGLWDAWGPWSECSRTCGGGASYSLRRC
LSSKSCEGRNIRYRTCSNVDCPPEAGDFRAQQCSAHNDVKHHGQFYEWLPVSNDPDNPCS
LKCQAKGTTLVVELAPKVLDGTRCYTESLDMCISGLCQIVGCDHQLGSTVKEDNCGVCNG
DGSTCRLVRGQYKSQLSATKSDDTVVALPYGSRHIRLVLKGPDHLYLETKTLQGTKGENS
LSSTGTFLVDNSSVDFQKFPDKEILRMAGPLTADFIVKIRNSGSADSTVQFIFYQPIIHR
WRETDFFPCSATCGGGYQLTSAECYDLRSNRVVADQYCHYYPENIKPKPKLQECNLDPCP
ASDGYKQIMPYDLYHPLPRWEATPWTACSSSCGGGIQSRAVSCVEEDIQGHVTSVEEWKC
MYTPKMPIAQPCNIFDCPKWLAQEWSPCTVTCGQGLRYRVVLCIDHRGMHTGGCSPKTKP
HIKEECIVPTPCYKPKEKLPVEAKLPWFKQAQELEEGAAVSEEPS

Important features:
Signal peptide:
amino acids 1-25

N-glycosylation site:
amino acids 251-254

Thrombospondin 1:
amino acids 385-399

von Willebrand factor type C domain proteins:
amino acids 385-399, 445-459 and 42-56

FIGURE 145

GGAGGAGGGAGGGCGGGCAGGCGCCAGCCCAGAGCAGCCCCGGGCACCAGCACGGACTCT
CTCTTCCAGCCCAGGTGCCCCCCACTCTCGCTCCATTCGGCGGGAGCACCCAGTCCTGTA
CGCCAAGGAACTGGTCCTGGGGGCACC**ATG**GTTTCGGCGGCAGCCCCCAGCCTCCTCATC
CTTCTGTTGCTGCTGCTGGGGTCTGTGCCTGCTACCGACGCCCGCTCTGTGCCCCTGAAG
GCCACGTTCCTGGAGGATGTGGCGGGTAGTGGGGAGGCCGAGGGCTCGTCGGCCTCCTCC
CCGAGCCTCCCGCCACCCTGGACCCCGGCCCTCAGCCCCACATCGATGGGGCCCCAGCCC
ACAACCCTGGGGGGCCCATCACCCCCCACCAACTTCCTGGATGGGATAGTGGACTTCTTC
CGCCAGTACGTGATGCTGATTGCTGTGGTGGGCTCCCTGGCCTTTCTGCTGATGTTCATC
GTCTGTGCCGCGGTCATCACCCGGCAGAAGCAGAAGGCCTCGGCCTATTACCCATCGTCC
TTCCCCAAGAAGAAGTACGTGGACCAGAGTGACCGGGCCGGGGGCCCCCGGGCCTTCAGT
GAGGTCCCCGACAGAGCCCCCGACAGCAGGCCCGAGGAAGCCCTGGATTCCTCCCGGCAG
CTCCAGGCCGACATCTTGGCCGCCACCCAGAACCTCAAGTCCCCCACCAGGGCTGCACTG
GGCGGTGGGGACGGAGCCAGGATGGTGGAGGGCAGGGGCGCAGAGGAAGAGGAGAAGGGC
AGCCAGGAGGGGGACCAGGAAGTCCAGGGACATGGGGTCCCAGTGGAGACACCAGAGGCG
CAGGAGGAGCCGTGCTCAGGGGTCCTTGAGGGGGCTGTGGTGGCCGGTGAGGGCCAAGGG
GAGCTGGAAGGGTCTCTCTTGTTAGCCCAGGAAGCCCAGGGACCAGTGGGTCCCCCCGAA
AGCCCCTGTGCTTGCAGCAGTGTCCACCCCAGTGTC**TAA**CAGTCCTCCCGGGCTGCCAGC
CCTGACTGTCGGGCCCCCAAGTGGTCACCTCCCCGTGTATGAAAAGGCCTTCAGCCCTGA
CTGCTTCCTGACACTCCCTCCTTGGCCTCCCTGTGGTGCCAATCCCAGCATGTGCTGATT
CTACAGCAGGCAGAAATGCTGGTCCCCGGTGCCCCGGAGGAATCTTACCAAGTGCCATCA
TCCTTCACCTCAGCAGCCCCAAAGGGCTACATCCTACAGCACAGCTCCCCTGACAAAGTG
AGGGAGGGCACGTGTCCCTGTGACAGCCAGGATAAAACATCCCCCAAAGTGCTGGGATTA
CAGGCGTGAGCCACCGTGCCCGGCCCAAACTACTTTTTAAAACAGCTACAGGGTAAAATC
CTGCAGCACCCACTCTGGAAAATACTGCTCTTAATTTTCCTGAAGGTGGCCCCCTGTTTC
TAGTTGGTCCAGGATTAGGGATGTGGGGTATAGGGCATTTAAATCCTCTCAAGCGCTCTC
CAAGCACCCCCGGCCTGGGGGTGAGTTTCTCATCCCGCTACTGCTGCTGGGATCAGGTTG
AATGAATGGAACTCTTCCTGTCTGGCCTCCAAAGCAGCCTAGAAGCTGAGGGGCTGTGTT
TGAGGGGACCTCCACCCTGGGGAAGTCCGAGGGGCTGGGGAAGGGTTTCTGACGCCCAGC
CTGGAGCAGGGGGGCCCTGGCCACCCCCTGTTGCTCACACATTGTCTGGCAGCCTGTGTC
CACAATATTCGTCAGTCCTCGACAGGGAGCCTGGGCTCCGTCCTGCTTTAGGGAGGCTCT
GGCAGGAGGTCCTCTCCCCCATCCCTCCATCTGGGGCTCCCCCAACCTCTGCACAGCTCT
CCAGGTGCTGAGATATAATGCACCAGCACAATAAACCTTTATTCCGGCCTGAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGA

FIGURE 146

MVSAAAPSLLILLLLLLGSVPATDARSVPLKATFLEDVAGSGEAEGSSASSPSLPPPWTP
ALSPTSMGPQPTTLGGPSPPTNFLDGIVDFFRQYVMLIAVVGSLAFLLMFIVCAAVITRQ
KQKASAYYPSSFPKKKYVDQSDRAGGPRAFSEVPDRAPDSRPEEALDSSRQLQADILAAT
QNLKSPTRAALGGGDGARMVEGRGAEEEEKGSQEGDQEVQGHGVPVETPEAQEEPCSGVL
EGAVVAGEGQGELEGSLLLAQEAQGPVGPPESPCACSSVHPSV

Signal peptide:
amino acids 1-25

Transmembrane domain:
amino acids 94-118

N-myristoylation site:
amino acids 18-24, 40-46, 46-52, 145-151, 192-198, 193-199, 211-217, 238-244, 242-248

FIGURE 147

GAAAGACGTGGTCCTGACAGACAGACAATCCTATTCCCTACCAAAATGAAGATGCTGCTG
CTGCTGTGTTTGGGACTGACCCTAGTCTGTGTCCATGCAGAAGAAGCTAGTTCTACGGGA
AGGAACTTTAATGTAGAAAAGATTAATGGGGAATGGCATACTATTATCCTGGCCTCTGAC
AAAAGAGAAAAGATAGAAGAACATGGCAACTTTAGACTTTTTCTGGAGCAAATCCATGTC
TTGGAGAATTCCTTAGTTCTTAAAGTCCATACTGTAAGAGATGAAGAGTGCTCCGAATTA
TCTATGGTTGCTGACAAAACAGAAAAGGCTGGTGAATATTCTGTGACGTATGATGGATTC
AATACATTTACTATACCTAAGACAGACTATGATAACTTTCTTATGGCTCACCTCATTAAC
GAAAAGGATGGGGAAACCTTCCAGCTGATGGGGCTCTATGGCCGAGAACCAGATTTGAGT
TCAGACATCAAGGAAAGGTTTGCACAACTATGTGAGGAGCATGGAATCCTTAGAGAAAAT
ATCATTGACCTATCCAATGCCAATCGCTGCCTCCAGGCCCGAGAATGAAGAATGGCCTGA
GCCTCCAGTGTTGAGTGGACACTTCTCACCAGGACTCCACCATCATCCCTTCCTATCCAT
ACAGCATCCCCAGTATAAATTCTGTGATCTGCATTCCATCCTGTCTCACTGAGAAGTCCA
ATTCCAGTCTATCAACATGTTACCTAGGATACCTCATCAAGAATCAAAGACTTCTTTAAA
TTTCTCTTTGATACACCCTTGACAATTTTTCATGAAATTATTCCTCTTCCTGTTCAATAA
ATGATTACCCTTGCACTTAA

FIGURE 148

MKMLLLLCLGLTLVCVHAEEASSTGRNFNVEKINGEWHTIILASDKREKIEEHGNFRLFL
EQIHVLENSLVLKVHTVRDEECSELSMVADKTEKAGEYSVTYDGFNTFTIPKTDYDNFLM
AHLINEKDGETFQLMGLYGREPDLSSDIKERFAQLCEEHGILRENIIDLSNANRCLQARE

FIGURE 149

GTGGACTCTGAGAAGCCCAGGCAGTTGAGGACAGGAGAGAGAAGGCTGCAGACCCAGAGG
GAGGGAGGACAGGGAGTCGGAAGGAGGAGGACAGAGGAGGGCACAGAGACGCAGAGCAAG
GGCGGCAAGGAGGAGACCCTGGTGGGAGGAAGACACTCTGGAGAGAGAGGGGGCTGGGCA
GAG<u>**ATG**</u>AAGTTCCAGGGGCCCCTGGCCTGCCTCCTGCTGGCCCTCTGCCTGGGCAGTGGG
GAGGCTGGCCCCCTGCAGAGCGGAGAGGAAAGCACTGGGACAAATATTGGGGAGGCCCTT
GGACATGGCCTGGGAGACGCCCTGAGCGAAGGGGTGGGAAAGGCCATTGGCAAAGAGGCC
GGAGGGGCAGCTGGCTCTAAAGTCAGTGAGGCCCTTGGCCAAGGGACCAGAGAAGCAGTT
GGCACTGGAGTCAGGCAGGTTCCAGGCTTTGGCGCAGCAGATGCTTTGGGCAACAGGGTC
GGGGAAGCAGCCCATGCTCTGGGAAACACTGGGCACGAGATTGGCAGACAGGCAGAAGAT
GTCATTCGACACGGAGCAGATGCTGTCCGCGGCTCCTGGCAGGGGGTGCCTGGCCACAGT
GGTGCTTGGGAAACTTCTGGAGGCCATGGCATCTTTGGCTCTCAAGGTGGCCTTGGAGGC
CAGGGCCAGGGCAATCCTGGAGGTCTGGGGACTCCGTGGGTCCACGGATACCCCGGAAAC
TCAGCAGGCAGCTTTGGAATGAATCCTCAGGGAGCTCCCTGGGGTCAAGGAGGCAATGGA
GGGCCACCAAACTTTGGGACCAACACTCAGGGAGCTGTGGCCCAGCCTGGCTATGGTTCA
GTGAGAGCCAGCAACCAGAATGAAGGGTGCACGAATCCCCCACCATCTGGCTCAGGTGGA
GGCTCCAGCAACTCTGGGGGAGGCAGCGGCTCACAGTCGGGCAGCAGTGGCAGTGGCAGC
AATGGTGACAACAACAATGGCAGCAGCAGTGGTGGCAGCAGCAGTGGCAGCAGCAGTGGC
AGCAGCAGTGGCGGCAGCAGTGGCGGCAGCAGTGGTGGCAGCAGTGGCAACAGTGGTGGC
AGCAGAGGTGACAGCGGCAGTGAGTCCTCCTGGGGATCCAGCACCGGCTCCTCCTCCGGC
AACCACGGTGGGAGCGGCGGAGGAAATGGACATAAACCCGGGTGTGAAAAGCCAGGGAAT
GAAGCCCGCGGGAGCGGGGAATCTGGGATTCAGGGCTTCAGAGGACAGGGAGTTTCCAGC
AACATGAGGGAAATAAGCAAAGAGGGCAATCGCCTCCTTGGAGGCTCTGGAGACAATTAT

FIGURE 150

MKFQGPLACLLLALCLGSGEAGPLQSGEESTGTNIGEALGHGLGDALSEGVGKAIGKEAG
GAAGSKVSEALGQGTREAVGTGVRQVPGFGAADALGNRVGEAAHALGNTGHEIGRQAEDV
IRHGADAVRGSWQGVPGHSGAWETSGGHGIFGSQGGLGGQGQGNPGGLGTPWVHGYPGNS
AGSFGMNPQGAPWGQGGNGGPPNFGTNTQGAVAQPGYGSVRASNQNEGCTNPPPSGSGGG
SSNSGGGSGSQSGSSGSGSNGDNNNGSSSGGSSSGSSSGSSSGGSSGGSSGGSSGNSGGS
RGDSGSESSWGSSTGSSSGNHGGSGGGNGHKPGCEKPGNEARGSGESGIQGFRGQGVSSN
MREISKEGNRLLGGSGDNYRGQGSSWGSGGGDAVGGVNTVNSETSPGMFNFDTFWKNFKS
KLGFINWDAINKDQRSSRIP

Signal peptide:
amino acids 1-21

N-glycosylation site:
amino acids 265-269

Glycosaminoglycan attachment site:
amino acids 235-239, 237-241, 244-248, 255-259, 324-328, 388-392

Casein kinase II phosphorylation site:
amino acids 26-30, 109-113, 259-263, 300-304, 304-308

N-myristoylation site:
amino acids 17-23, 32-38, 42-48, 50-56, 60-66, 61-67, 64-70, 74-80, 90-96, 96-102, 130-136, 140-146, 149-155, 152-158, 155-161, 159-165, 163-169, 178-184, 190-196, 194-200, 199-205, 218-224, 236-242, 238-244, 239-245, 240-246, 245-251, 246-252, 249-252, 253-259, 256-262, 266-272, 270-276, 271-277, 275-281, 279-285, 283-289, 284-290, 287-293, 288-294, 291-297, 292-298, 295-301, 298-304, 305-311, 311-317, 315-321, 319-325, 322-328, 323-329, 325-331, 343-349, 354-360, 356-362, 374-380, 381-387, 383-389, 387-393, 389-395, 395-401

Cell attachment sequence:
amino acids 301-304

FIGURE 151

CGGCCACAGCTGGCATGCTCTGCCTGATCGCCATCCTGCTGTATGTCCTCGTCCAGTACC
TCGTGAACCCCGGGGTGCTCCGCACGGACCCCAGATGTCAAGAAT<u>ATG</u>AACACGTGGCTG
CTGTTCCTCCCCCTGTTCCCGGTGCAGGTGCAGACCCTGATAGTCGTGATCATCGGGATG
CTCGTGCTCCTGCTGGACTTTCTTGGCTTGGTGCACCTGGGCCAGCTGCTCATCTTCCAC
ATCTACCTGAGTATGTCCCCCACCCTAAGCCCCCGATCCCCCCAAGGCTGGGTGGTCAGA
GCTGCTCATCTTACACCTCTACTTGAGTATGTCCCTAACCCTGAGCCCCCCACGCCTGGG
GCCAGAGTCTTTGTCCCCCGTGTGCGCATGTGTTCAGGGTCAGCCTCTCCCAGAAGTGAG
ATCATGGACAAAAAGGGCAAATCACAGGAAGAAATTAAATCCATGAGGACCCAGCAGGCC
CAGCAAGAAGCTGAACTCACGCCGAGACCTGCAGGAGTGGTGCCAGGTGCT<u>TGA</u>AGTAAC
AAGTTTAAAATGTTCAGAGACAATGGAATGGAATCTATTAGGCAAGAACAGGACATTATG
AAATAAGGACAGGTGGACTTCCAAAAACACAAGTAGAAATTCTAACAATGAAATATATTA
CAGGCAGGTCACCCACTAACCAAACAACTGAAGCGAGAGCTGTGGTCTTGCTTGGTCTCA
CAGTGGGCACAGCGGTAGGCGGTCAGTCATGTTGCTGAACGACGGAGGGTAAACTCCCCA
GCCCCAAGAAAACCTGTGTTGGAAGTAACAACAACCTCCCTGCTCCTGGCACCAGCCGTT
TTGGTCATGGTGGGCCAGCTGCAAAGCGTCTTCCATTCTCTGGGCAGTGGTGGCCCCGAG
GCTGTGGCCTCTCAGGGGGTTTCTGTGGACACGGGCAGCAGAGTGTGTCCAGGCCAGCCC
CCAAGAATGCCCTGCTCCTGACAGCTTGGCCAACCCCTGGTCAGGGCAGAGGGAGTTGGG
TGGGTCAGGCTCTGGGCTCACCTCCATCTCCAGAGCATCCCCTGCCTGCAGTTGTGGCAA
GAACGCCCAGCTCAGAATGAACACACCCCACCAAGAGCCTCCTTGTTCATAACCACAGGT
TACCCTACAAACCACTGTCCCCACACAACCCTGGGGATGTTTTAAAACACACACCTCTAA
CGCATATCTTACAGTCACTGTTGTCTTGCCTGAGGGTTGAATTTTTTTAATGAAAGTGC
AATGAAAATCACTGGATTAAATCCTACGGACACAGAGCTGAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAA

FIGURE 152

MNTWLLFLPLFPVQVQTLIVVIIGMLVLLLDFLGLVHLGQLLIFHIYLSMSPTLSPRSPQ
GWVVRAAHLTPLLEYVPNPEPPTPGARVFVPRVRMCSGSASPRSEIMDKKGKSQEEIKSM
RTQQAQQEAELTPRPAGVVPGA

FIGURE 153

AACTGGAAGGAAAGAAAGAAAGGTCAGCTTTGGCCCAG<u>ATG</u>TGGTTACCCCTTGGTCTCC
TGTCTTTATGTCTTTCTCCTCTTCCTATTCTGTCATCTCCCTCACTTAAGTCTCAGGCCT
GTCAGCAGCTCCTGTGGACATTGCCATCCCCTCTGGTAGCCTTCAGAGCAAACAGGACAA
CCTATGTTATGGATGTTTCCACCAACCAGGGTAGTGGCATGGAGCACCGTAACCATCTGT
GCTTCTGTGATCTCTATGACAGAGCCACTTCTCCACCTCTGAAATGTTCCCTGCTCTGAA
ATCTGGCATGAGATGGCACAGGTGACCACGCAGAAGCCACCAGAATCTTGCCTGCCCTAT
TCCTCCTCCCAAGTCTGTTCTCTTATTGTCAACCTCAGCACAACAGGCTGGCGCCAATGG
CATTACAGAGAAAGCAATCTGTGTGGCTAGTGGGCAGATTACCATGCAAGCCCCAGGAGA
AATGGAGGAGCTTTGTAGCCACCTCCCTGTCAGCCAGTATTAACATGTCCCCTTCCCCCT
GCCCCGCCGTAGATTCAGGACATTCGCCCCTGTGTGCCACCAAACCAGGACTTTCCCCTT
GGCTTGGCATCCCTGGCTCTCTCCTGGTACCCAGCAAGACGTCTGTTCCAGGGCAGTGTA
GCATCTTTCAAGCTCCGTTACTATGGCGATGGCCATGATGTTACAATCCCACTTGCCTGA
ATAATCAAGTGGGAAGGGGAAGCAGAGGGAAATGGGGCCATGTGAATGCAGCTGCTCTGT
TCTCCCTACCCTGAGGAAAAACCAAAGGGAAGCAACAGGAACTTCTGCAACTGGTTTTTA
TCGGAAAGATCATCCTGCCTGCAGATGCTGTTGAAGGGGCACAAGAAATGTAGCTGGAGA
AGATTGATGAAAGTGCAGGTGTGTAAGGAAATAGAACAGTCTGCTGGGAGTCAGACCTGG
AATTCTGATTCCAAACTCTTTATTACTTTGGGAAGTCACTCAGCCTCCCCGTAGCCATCT
CCAGGGTGACGGAACCCAGTGTATTACCTGCTGGAACCAAGGAAACTAACAATGTAGGTT
ACTAGTGAATACCCCAATGGTTTCTCCAATTATGCCCATGCCACCAAAACAATAAAACAA
AATTCTCTAACACTGAAA

FIGURE 154

MWLPLGLLSLCLSPLPILSSPSLKSQACQQLLWTLPSPLVAFRANRTTYVMDVSTNQGSG
MEHRNHLCFCDLYDRATSPPLKCSLL

FIGURE 155

GTAGCGCGTCTTGGGTCTCCCGGCTGCCGCTGCTGCCGCCGCCGCCTCGGGTCGTGGAGC
CAGGAGCGACGTCACCGCCATGGCAGGCATCAAAGCTTTGATTAGTTTGTCCTTTGGAGG
AGCAATCGGACTGATGTTTTTGATGCTTGGATGTGCCCTTCCAATATACAACAAATACTG
GCCCCTCTTTGTTCTATTTTTTACATCCTTTCACCTATTCCATACTGCATAGCAAGAAG
ATTAGTGGATGATACAGATGCTATGAGTAACGCTTGTAAGGAACTTGCCATCTTTCTTAC
AACGGGCATTGTCGTGTCAGCTTTTGGACTCCCTATTGTATTTGCCAGAGCACATCTGAT
TGAGTGGGGAGCTTGTGCACTTGTTCTCACAGGAAACACAGTCATCTTTGCAACTATACT
AGGCTTTTTCTTGGTCTTTGGAAGCAATGACGACTTCAGCTGGCAGCAGTGGTGAAAAGA
AATTACTGAACTATTGTCAAATGGACTTCCTGTCATTTGTTGGCCATTCACGCACACAGG
AGATGGGGCAGTTAATGCTGAATGGTATAGCAAGCCTCTTGGGGGTATTTTAGGTGCTCC
CTTCTCACTTTTATTGTAAGCATACTATTTTCACAGAGACTTGCTGAAGGATTAAAAGGA
TTTTCTCTTTTGGAAAAGCTTGACTGATTTCACACTTATCTATAGTATGCTTTTTGTGGT
GTCCTGCTGAATTTAAATATTTATGTGTTTTTCCTGTTAGGTTGATTTTTTTTGGAATCA
ATATGCAATGTTAAACACTTTTTTAATGTAATCATTTGCATTGGTTAGGAATTCAGAATT
CCGCCGGCTCTATTACTGGTCAAGTACATCTTTTCTCTTAAAATTATTTAGCCTCCATTA
TTACAAAAAATTATAAAAATAAGTTTTCAGTCAGTCAGGATGACATCACTCCCAATGTTA
TGCAGACATACAGACGGTTGGCATACGTTATAGACTGTATACTCAGTGCAAATATAGCTG
CATTTATACCTCAGAGGGGCCAAGTGTTAATGCCCATGCCCTCCGTTAAGGGTTGTTGGT
TTTACTGGTAGACAGATGTTTTGTGGATTGAAAATTATTTTATGGAATTGCTACAGAGGA
GTGCTTTTCTTCTCAATTGTTAGAAGAATTTATGTTAAACTTTAAGGTAAGGGTGTAAAA
ACATTTTTGAGATAAGGTTTTTATTTATGTTTATTATTGTTAGAGTGAGTTGCAATGTGG
GAAGAAATGACATTGAAATTCCAGTTTTTGAATCCTGTTTCTATTTATAAGTGAAATTTG
TGATCTCCTATCAACCTTTCATGTTTTACCCTGTTAAAATGGACATACATGGAACCACTA
CTGATGAGGGACAGTTGTATGTTTGCATCATATATGCCAGAAAACCTTCCTCTGCTTCCT
CCTTTTGACTTATTTGGTATGTTGTATATATTACATAAAATAACTTTTCAAATATAGTTT
AATAACACTTAGAAGTGTTTACTTACCTGGAAAATAATTGCTATGCCGTACATTCAGAGT
GCCCCCTCCCCTGCAAGGCCTTGCCATGATTAACAAGTAACTTGTTAGTCTTACAGATAA
TTCATGCATTAACAGTTTAAGATTTAGACCATGGTAATAGTAGTTCTTATTCTCTAAGGT
TATATCATATGTAATTTAAAAGTATTTTTAAGACAAGTTTCCTGTATACCTCTGAACTGT
TTTGATTTTGAGTTCATCATGATAGATCTGCTGTTTCCTTATAAAAGGCATTTGTTGTGT
GAGTTAATGCAAAGTAGCCAAGTCCAGCTATATAGCAGCTTCAGAAACATACCTGACCAA
AAAATTCCCAGTAACCAGGCATGATCAATTTATAGTGGTCGTTTACATCTAATAATTATC
AGGACTTTTTTCAGGAGTGGGTTATAAAAACATTCAAGTTGGTCTGACAGTATTTTGTTA
AGGATATTTGTTTGTATGTTTATTCAGTATACTTACATAAAAATTATTTCGCCATCAGCC
AAAACTCAGTAATCATGACAGCTGTCTGTTGTTTTATGAAGTTTATTTCTCAAGAAAATG
GGAATAAATTTGGGATTTGTTCAGCTTTTTTACTAAAGATGCCTAAAGCCACAGGTTTTA
TTGCCTAACTTAAGCCATGACTTTTAGATATGAGATGACGGGAAGCAGGACGAAATATCG
GCGTGTGGCTGGAGCCTTCCCACTGGAGGCTGAAAGTGGCTTGTGGTATTATAATGTTCA
GATTTCAAGAGGAAGGTGCAGGTACACATGAGTTAGAGAGCTGGTGAGACAGTTGGGAAC
TCTTTGTGCTTGTGATCTACTGGACTTTTTTTTTGCAGGAAGTGCATTCTCTGGTCCTTC
CCTATTTTCTGTTCTGGATGTCAGTGCAGTGCACTGCTACTGTTTTATCCACTTGGCCAC
AGACTTTTTCTAACAGCTGCGTATTATTTCTATATACTAATTGCATTGGCAGCATTGTGT
CTTTGACCTTGTATACTAGCTTGACATAGTGCTGTCTCTGATTTCTAGGCTAGTTACTTG
AGATATGAATTTTCCATAGAATATGCACTGATACAACATTACCATTCTTCTATGGAAAGA
AAACTTTTGATGATGAAACAATAAAGATTTTAAATATCTATTTAAAAAAAAAA

FIGURE 156

MAGIKALISLSFGGAIGLMFLMLGCALPIYNKYWPLFVLFFYILSPIPYCIARRLVDDTD
AMSNACKELAIFLTTGIVVSAFGLPIVFARAHLIEWGACALVLTGNTVIFATILGFFLVF
GSNDDFSWQQW

FIGURE 157

GTTTCTCATAGTTGGCGTCTTCTAAAGGAAAAACACTAAAATGAGGAACTCAGCGGACCG
GGAGCGACGCAGCTTGAGGGAAGCATCCCTAGCTGTTGGCGCAGAGGGGCGAGGCTGAAG
CCGAGTGGCCCGAGGTGTCTGAGGGGCTGGGGCAAAGGTGAAAGAGTTTCAGAACAAGCT
TCCTGGAACCCATGACCCATGAAGTCTTGTCGACATTTATACCGTCTGAGGGTAGCAGCT
CGAAACTAGAAGAAGTGGAGTGTTGCCAGGGACGGCAGTATCTCTTTGTGTGACCCTGGC
GGCCTATGGGACGTTGGCTTCAGACCTTTGTGATACACCATGCTGCGTGGGACGATGACG
GCGTGGAGAGGAATGAGGCCTGAGGTCACACTGGCTTGCCTCCTCCTAGCCACAGCAGGC
TGCTTTGCTGACTTGAACGAGGTCCCTCAGGTCACCGTCCAGCCTGCGTCCACCGTCCAG
AAGCCCGGAGGCACTGTGATCTTGGGCTGCGTGGTGGAACCTCCAAGGATGAATGTAACC
TGGCGCCTGAATGGAAAGGAGCTGAATGGCTCGGATGATGCTCTGGGTGTCCTCATCACC
CACGGGACCCTCGTCATCACTGCCCTTAACAACCACACTGTGGGACGGTACCAGTGTGTG
GCCCGGATGCCTGCGGGGGCTGTGGCCAGCGTGCCAGCCACTGTGACACTAGCCAATCTC
CAGGACTTCAAGTTAGATGTGCAGCACGTGATTGAAGTGGATGAGGGAAACACAGCAGTC
ATTGCCTGCCACCTGCCTGAGAGCCACCCCAAAGCCCAGGTCCGGTACAGCGTCAAACAA
GAGTGGCTGGAGGCCTCCAGAGGTAACTACCTGATCATGCCCTCAGGGAACCTCCAGATT
GTGAATGCCAGCCAGGAGGACGAGGGCATGTACAAGTGTGCAGCCTACAACCCAGTGACC
CAGGAAGTGAAAACCTCCGGCTCCAGCGACAGGCTACGTGTGCGCCGCTCCACCGCTGAG
GCTGCCCGCATCATCTACCCCCCAGAGGCCCAAACCATCATCGTCACCAAAGGCCAGAGT
CTCATTCTGGAGTGTGTGGCCAGTGGAATCCCACCCCCACGGGTCACCTGGGCCAAGGAT
GGGTCCAGTGTCACCGGCTACAACAAGACGCGCTTCCTGCTGAGCAACCTCCTCATCGAC
ACCACCAGCGAGGAGGACTCAGGCACCTACCGCTGCATGGCCGACAATGGGGTTGGGCAG
CCCGGGGCAGCGGTCATCCTCTACAATGTCCAGGTGTTTGAACCCCCTGAGGTCACCATG
GAGCTATCCCAGCTGGTCATCCCCTGGGGCCAGAGTGCCAAGCTTACCTGTGAGGTGCGT
GGGAACCCCCCGCCCTCCGTGCTGTGGCTGAGGAATGCTGTGCCCCTCATCTCCAGCCAG
CGCCTCCGGCTCTCCCGCAGGGCCCTGCGCGTGCTCAGCATGGGGCCTGAGGACGAAGGC
GTCTACCAGTGCATGGCCGAGAACGAGGTTGGGAGCGCCCATGCCGTAGTCCAGCTGCGG
ACCTCCAGGCCAAGCATAACCCCAAGGCTATGGCAGGATGCTGAGCTGGCTACTGGCACA
CCTCCTGTATCACCCTCCAAACTCGGCAACCCTGAGCAGATGCTGAGGGGGCAACCGGCG
CTCCCCAGACCCCCAACGTCAGTGGGGCCTGCTTCCCCGAAGTGTCCAGGAGAGAAGGGG
CAGGGGGCTCCCGCCGAGGCTCCCATCATCCTCAGCTCGCCCCGCACCTCCAAGACAGAC
TCATATGAACTGGTGTGGCGGCCTCGGCATGAGGGCAGTGGCCGGGCGCCAATCCTCTAC
TATGTGGTGAAACACCGCAAGCAGGTCACAAATTCCTCTGACGATTGGACCATCTCTGGC
ATTCCAGCCAACCAGCACCGCCTGACCCTCACCAGACTTGACCCCGGGAGCTTGTATGAA
GTGGAGATGGCAGCTTACAACTGTGCGGGAGAGGGCCAGACAGCCATGGTCACCTTCCGA
ACTGGACGGCGGCCCAAACCCGAGATCATGGCCAGCAAAGAGCAGCAGATCCAGAGAGAC
GACCCTGGAGCCAGTCCCCAGAGCAGCAGCCAGCCAGACCACGGCCGCCTCTCCCCCCCA
GAAGCTCCCGACAGGCCCACCATCTCCACGGCCTCCGAGACCTCAGTGTACGTGACCTGG
ATTCCCCGTGGGAATGGTGGGTTCCCAATCCAGTCCTTCCGTGTGGAGTACAAGAAGCTA
AAGAAAGTGGGAGACTGGATTCTGGCCACCAGCGCCATCCCCCCATCGCGGCTGTCCGTG
GAGATCACGGGCCTAGAGAAAGGCACCTCCTACAAGTTTCGAGTCCGGGCTCTGAACATG
CTGGGGGAGAGCGAGCCCAGCGCCCCCTCTCGGCCCTACGTGGTGTCGGGCTACAGCGGT
CGCGTGTACGAGAGGCCCGTGGCAGGTCCTTATATCACCTTCACGGATGCGGTCAATGAG
ACCACCATCATGCTCAAGTGGATGTACATCCCAGCAAGTAACAACAACACCCCAATCCAT
GGCTTTTATATCTATTATCGACCCACAGACAGTGACAATGATAGTGACTACAAGAAGGAT
ATGGTGGAAGGGGACAAGTACTGGCACTCCATCAGCCACCTGCAGCCAGAGACCTCCTAC
GACATTAAGATGCAGTGCTTCAATGAAGGAGGGGAGAGCGAGTTCAGCAACGTGATGATC
TGTGAGACCAAAGCTCGGAAGTCTTCTGGCCAGCCTGGTCGACTGCCACCCCCAACTCTG
GCCCCACCACAGCCGCCCCTTCCTGAAACCATAGAGCGGCCGGTGGGCACTGGGGCCATG
GTGGCTCGCTCCAGCGACCTGCCCTATCTGATTGTCGGGGTCGTCCTGGGCTCCATCGTT
CTCATCATCGTCACCTTCATCCCCTTCTGCTTGTGGAGGGCCTGGTCTAAGCAAAAACAT
ACAACAGACCTGGGTTTTCCTCGAAGTGCCCTTCCACCCTCCTGCCCGTATACTATGGTG
CCATTGGGAGGACTCCCAGGCCACCAGGCCAGTGGACAGCCCTACCTCAGTGGCATCAGT

GGACGGGCCTGTGCTAATGGGATCCACATGAATAGGGGCTGCCCCTCGGCTGCAGTGGGC
TACCCGGGCATGAAGCCCCAGCAGCACTGCCCAGGCGAGCTTCAGCAGCAGAGTGACACC
AGCAGCCTGCTGAGGCAGACCCATCTTGGCAATGGATATGACCCCCAAAGTCACCAGATC
ACGAGGGGTCCCAAGTCTAGCCCGGACGAGGGCTCTTTCTTATACACACTGCCCGACGAC
TCCACTCACCAGCTGCTGCAGCCCCATCACGACTGCTGCCAACGCCAGGAGCAGCCTGCT
GCTGTGGGCCAGTCAGGGGTGAGGAGAGCCCCCGACAGTCCTGTCCTGGAAGCAGTGTGG
GACCCTCCATTTCACTCAGGGCCCCCATGCTGCTTGGGCCTTGTGCCAGTTGAAGAGGTG
GACAGTCCTGACTCCTGCCAAGTGAGTGGAGGAGACTGGTGTCCCCAGCACCCCGTAGGG
GCCTACGTAGGACAGGAACCTGGAATGCAGCTCTCCCCGGGGCCACTGGTGCGTGTGTCT
TTTGAAACACCACCTCTCACAATT**TAG**GCAGAAGCTGATATCCCAGAAAGACTATATATT
GTTTTTTTTTTAAAAAAAAAAGAAGAAAAAAGAGACAGAGAAAATTGGTATTTATTTTTC
TATTATAGCCATATTTATATATTTATGCACTTGTAAATAAATGTATATGTTTTATAATTC
TGGAGAGACATAAGGAGTCCTACCCGTTGAGGTTGGAGAGGGAAAATAAAGAAGCTGCCA
CCTAACAGGAGTCACCCAGGAAAGCACCGCACAGGCTGGCGCGGGACAGACTCCTAACCT
GGGGCCTCTGCAGTGGCAGGCGAGGCTGCAGGAGGCCCACAGATAAGCTGGCAAGAGGAA
GGATCCCAGGCACATGGTTCATCACGAGCATGAGGGAACAGCAAGGGGCACGGTATCACA
GCCTGGAGACACCCACACAGATGGCTGGATCCGGTGCTACGGGAAACATTTTCCTAAGAT
GCCCATGAGAACAGACCAAGATGTGTACAGCACTATGAGCATTAAAAAACCTTCCAGAAT
CAATAATCCGTGGCAACATATCTCTGTAAAAACAAACACTGTAACTTCTAAATAAATGTT
TAGTCTTCCCTGTAAAA

FIGURE 158

MLRGTMTAWRGMRPEVTLACLLLATAGCFADLNEVPQVTVQPASTVQKPGGTVILGCVVE
PPRMNVTWRLNGKELNGSDDALGVLITHGTLVITALNNHTVGRYQCVARMPAGAVASVPA
TVTLANLQDFKLDVQHVIEVDEGNTAVIACHLPESHPKAQVRYSVKQEWLEASRGNYLIM
PSGNLQIVNASQEDEGMYKCAAYNPVTQEVKTSGSSDRLRVRRSTAEAARIIYPPEAQTI
IVTKGQSLILECVASGIPPPRVTWAKDGSSVTGYNKTRFLLSNLLIDTTSEEDSGTYRCM
ADNGVGQPGAAVILYNVQVFEPPEVTMELSQLVIPWGQSAKLTCEVRGNPPPSVLWLRNA
VPLISSQRLRLSRRALRVLSMGPEDEGVYQCMAENEVGSAHAVVQLRTSRPSITPRLWQD
AELATGTPPVSPSKLGNPEQMLRGQPALPRPPTSVGPASPKCPGEKGQGAPAEAPIILSS
PRTSKTDSYELVWRPRHEGSGRAPILYYVVKHRKQVTNSSDDWTISGIPANQHRLTLTRL
DPGSLYEVEMAAYNCAGEGQTAMVTFRTGRRPKPEIMASKEQQIQRDDPGASPQSSSQPD
HGRLSPPEAPDRPTISTASETSVYVTWIPRGNGGFPIQSFRVEYKKLKKVGDWILATSAI
PPSRLSVEITGLEKGTSYKFRVRALNMLGESEPSAPSRPYVVSGYSGRVYERPVAGPYIT
FTDAVNETTIMLKWMYIPASNNNTPIHGFYIYYRPTDSDNDSDYKKDMVEGDKYWHSISH
LQPETSYDIKMQCFNEGGESEFSNVMICETKARKSSGQPGRLPPPTLAPPQPPLPETIER
PVGTGAMVARSSDLPYLIVGVVLGSIVLIIVTFIPFCLWRAWSKQKHTTDLGFPRSALPP
SCPYTMVPLGGLPGHQASGQPYLSGISGRACANGIHMNRGCPSAAVGYPGMKPQQHCPGE
LQQQSDTSSLLRQTHLGNGYDPQSHQITRGPKSSPDEGSFLYTLPDDSTHQLLQPHHDCC
QRQEQPAAVGQSGVRRAPDSPVLEAVWDPPFHSGPPCCLGLVPVEEVDSPDSCQVSGGDW
CPQHPVGAYVGQEPGMQLSPGPLVRVSFETPPLTI

Signal peptide:
amino acids 1-30

Transmembrane domain:
amino acids 16-30 (type II), 854-879

FIGURE 159

CCCACGCGTCCGCCCACGCGTCCGCCCACGCGTCCGCCCACGCGTCCGCCCACGCGTCCG
CCCACGCGTCCGCCCACGCGTCCGGTGCAAGCTCGCGCCGCACACTGCCTGGTGGAGGGA
AGGAGCCCGGGCGCCTCTCGCCGCTCCCCGCGCCGCCGTCCGCACCTCCCCACCGCCCGC
CGCCCGCCGCCCGCCGCCCGCAAAGCATGAGTGAGCCCGCTCTCTGCAGCTGCCCGGGGC
GCGAATGGCAGGCTGTTTCCGCGGAGTAAAAGGTGGCGCCGGTCAGTGGTCGTTTCCAAT
GACGGACATTAACCAGACTGTCAGATCCTGGGGAGTCGCGAGCCCCGAGTTTGGAGTTTT
TTCCCCCCACAACGTCACAGTCCGAACTGCAGAGGGAAAGGAAGGCGGCAGGAAGGCGAA
GCTCGGGCTCCGGCACGTAGTTGGGAAACTTGCGGGTCCTAGAAGTCGCCTCCCCGCCTT
GCCGGCCGCCCTTGCAGCCCCGAGCCGAGCAGCAAAGTGAGACATTGTGCGCCTGCCAGA
TCCGCCGGCCGCGGACCGGGGCTGCCTCGGAAACACAGAGGGGTCTTCTCTCGCCCTGCA
TATAATTAGCCTGCACACAAAGGGAGCAGCTGAATGGAGGTTGTCACTCTCTGGAAAAGG
ATTTCTGACCGAGCGCTTCCAATGGACATTCTCCAGTCTCTCTGGAAAGATTCTCGCTA<u>A</u>
<u>TG</u>GATTTCCTGCTGCTCGGTCTCTGTCTATACTGGCTGCTGAGGAGGCCCTCGGGGGTGG
TCTTGTGTCTGCTGGGGGCCTGCTTTCAGATGCTGCCCGCCGCCCCCAGCGGGTGCCCGC
AGCTGTGCCGGTGCGAGGGGCGGCTGCTGTACTGCGAGGCGCTCAACCTCACCGAGGCGC
CCCACAACCTGTCCGGCCTGCTGGGCTTGTCCCTGCGCTACAACAGCCTCTCGGAGCTGC
GCGCCGGCCAGTTCACGGGGTTAATGCAGCTCACGTGGCTCTATCTGGATCACAATCACA
TCTGCTCCGTGCAGGGGGACGCCTTTCAGAAACTGCGCCGAGTTAAGGAACTCACGCTGA
GTTCCAACCAGATCACCCAACTGCCCAACACCACCTTCCGGCCCATGCCCAACCTGCGCA
GCGTGGACCTCTCGTACAACAAGCTGCAGGCGCTCGCGCCCGACCTCTTCCACGGGCTGC
GGAAGCTCACCACGCTGCATATGCGGGCCAACGCCATCCAGTTTGTGCCCGTGCGCATCT
TCCAGGACTGCCGCAGCCTCAAGTTTCTCGACATCGGATACAATCAGCTCAAGAGTCTGG
CGCGCAACTCTTTCGCCGGCTTGTTTAAGCTCACCGAGCTGCACCTCGAGCACAACGACT
TGGTCAAGGTGAACTTCGCCCACTTCCCGCGCCTCATCTCCCTGCACTCGCTCTGCCTGC
GGAGGAACAAGGTGGCCATTGTGGTCAGCTCGCTGGACTGGGTTTGGAACCTGGAGAAAA
TGGACTTGTCGGGCAACGAGATCGAGTACATGGAGCCCCATGTGTTCGAGACCGTGCCGC
ACCTGCAGTCCCTGCAGCTGGACTCCAACCGCCTCACCTACATCGAGCCCCGGATCCTCA
ACTCTTGGAAGTCCCTGACAAGCATCACCCTGGCCGGGAACCTGTGGGATTGCGGGCGCA
ACGTGTGTGCCCTAGCCTCGTGGCTCAGCAACTTCCAGGGGCGCTACGATGGCAACTTGC
AGTGCGCCAGCCCGGAGTACGCACAGGGCGAGGACGTCCTGGACGCCGTGTACGCCTTCC
ACCTGTGCGAGGATGGGGCCGAGCCCACCAGCGGCCACCTGCTCTCGGCCGTCACCAACC
GCAGTGATCTGGGGCCCCCTGCCAGCTCGGCCACCACGCTCGCGGACGGCGGGGAGGGGC
AGCACGACGGCACATTCGAGCCTGCCACCGTGGCTCTTCCAGGCGGCGAGCACGCCGAGA
ACGCCGTGCAGATCCACAAGGTGGTCACGGGCACCATGGCCCTCATCTTCTCCTTCCTCA
TCGTGGTCCTGGTGCTCTACGTGTCCTGGAAGTGTTTCCCAGCCAGCCTCAGGCAGCTCA
GACAGTGCTTTGTCACGCAGCGCAGGAAGCAAAAGCAGAAACAGACCATGCATCAGATGG
CTGCCATGTCTGCCCAGGAATACTACGTTGATTACAAACCGAACCACATTGAGGGAGCCC
TGGTGATCATCAACGAGTATGGCTCGTGTACCTGCCACCAGCAGCCCGCGAGGGAATGCG
AGGTG<u>TGA</u>TTGTCCCAGTGGCTCTCAACCCATGCGCTACCAAATACGCCTGGGCAGCCGG
GACGGGCCGGCGGGCACCAGGCTGGGGTCTCCTTGTCTGTGCTCTGATATGCTCCTTGAC
TGAAACTTTAAGGGGATCTCTCCCAGAGACTTGACATTTTAGCTTTATTGTGTCTTAAAA
ACAAAAGCGAATTAAAACACAACAAAAAACCCCACCCCACAACCTTCAGGACAGTCTATC
TTAAATTTCATATGAGAACTCCTTCCTCCCTTTGAAGATCTGTCCATATTCAGGAATCTG
AGAGTGTAAAAAAGGTGGCCATAAGACAGAGAGAGAATAATCGTGCTTTGTTTTATGCTA
CTCCTCCCACCCTGCCCATGATTAAACATCATGTATGTAGAAGATCTTAAGTCCATACGC
ATTTCATGAAGAACCATTGGAAAGAGGAATCTGCAATCTGGGAGCTTAAGAGCAAATGAT

GACCATAGAAAGCTATGTTCTTACTTTGTGTGTGTGTCTGTATGTTTCTGCGTTGTGTGT
CTTTGTAGGCAAGCAAACGTTGTCTACACAAACGGGAATTTAGCTCACATCATTTCATGC
CCCTGTGCCTCTAGCTCTGGAGATTGGTGGGGGGAGGTGGGGGGAAACGGCAGGAATAAG
GGAAAGTGGTAGTTTTAACTAAGGTTTTGTAACACTTGAAATCTTTTCTTTCTCAAATTA
ATTATCTTTAAGCTTCAAGAAACTTGCTCTGACCCCTCTAAGCAAACTACTAAGCATTTA
AAAGAGAATCTAATTTTTAAAGGTGTAGCACCTTTTTTTTTATTCTTCCCACAGAGGGTG
CTAATCTCATTATGCTGTGCTATCTGAAAAGAACTTAAGGCCACAATTCACGTCTCGTCC
TGGGCATTGTGATGGATTGACCCTCCATTTGCAGTACCTTCCCAGCTGATTAAAGTTCAG
CAGTGGTATTGAGGTTTTTCGAATATTTATATAGAAAAAAAGTCTTTTCACATGACAAAT
GACACTCTCACACCAGTCTTAGCCCTAGTAGTTTTTTAGGTTGGACCAGAGGAAGCAGGT
TAAATGAGACCTGTCCTCTGCTGCACTCAGAAAAAAATAGGCAGTCCCTGATGCTCAGATC
TTAGCCTTGATATTAATAGTTGAGACCACCTACCCACAATGCAGCCTATACTCCCAAGAC
TACAAAGTTACCATCGCAAAGGAAAGGTTATTCCAGTAAAAGGAAATAGTTTTCTCAACC
ATTTAAAAATATTCTTCTGAACTCATCAAAGTAGAAGAGCCCCCAACCTTTTCTCTCTGC
CTTCAAGAAGGCAGACATTTGGTATGATTTAGCATCAACAACACATTTATGAGTATATGT
AAGTAATCAGAGGGGCAAATGCCACTTGTTATTCCTCCCAAGTTTTCCAAGCAAGTACAC
ACAGATCTCTGGTAGGATTAGGGGCCACTTGTGTTTCCGGCTTATTTTAGTCGACTTGTC
AGCAAGTTTGATGCCTAGTCTATCTGACATGGCCCAGTAGAACAGGGCATTGATGGATCA
CATGAGATGGTAGAAGGAACATCATCACATACCCCTCTCACAGAGAAAATTATCAAAGAA
CCAGAAATTATATCTGTTTTGGAGCAAGAGTGTCATAATGTTTCAGGGTAGTCAAAATAA
ACATAAATTATCTCCTCTAGATGAGTGGCGATGTTGGCTGATTTGGGTCTGCCATTGACA
GAATGTCAAATAAAAAGGAATTAGCTAGAATATGACCATTAAATGTGCTTCTGAAATATA
TTTTGAGATAGGTTTAGAATGTCA

FIGURE 160

MDFLLLGLCLYWLLRRPSGVVLCLLGACFQMLPAAPSGCPQLCRCEGRLLYCEALNLTEA
PHNLSGLLGLSLRYNSLSELRAGQFTGLMQLTWLYLDHNHICSVQGDAFQKLRRVKELTL
SSNQITQLPNTTFRPMPNLRSVDLSYNKLQALAPDLFHGLRKLTTLHMRANAIQFVPVRI
FQDCRSLKFLDIGYNQLKSLARNSFAGLFKLTELHLEHNDLVKVNFAHFPRLISLHSLCL
RRNKVAIVVSSLDWVWNLEKMDLSGNEIEYMEPHVFETVPHLQSLQLDSNRLTYIEPRIL
NSWKSLTSITLAGNLWDCGRNVCALASWLSNFQGRYDGNLQCASPEYAQGEDVLDAVYAF
HLCEDGAEPTSGHLLSAVTNRSDLGPPASSATTLADGGEGQHDGTFEPATVALPGGEHAE
NAVQIHKVVTGTMALIFSFLIVVLVLYVSWKCFPASLRQLRQCFVTQRRKQKQKQTMHQM
AAMSAQEYYVDYKPNHIEGALVIINEYGSCTCHQQPARECEV

FIGURE 161

GGCCGCCTGGAATTGTGGGAGTTGTGTCTGCCACTCGGCTGCCGGAGGCCGAAGGTCCGT
GACT<u>**ATG**</u>GCTCCCCAGAGCCTGCCTTCATCTAGGATGGCTCCTCTGGGCATGCTGCTTGG
GCTGCTGATGGCCGCCTGCTTCACCTTCTGCCTCAGTCATCAGAACCTGAAGGAGTTTGC
CCTGACCAACCCAGAGAAGAGCAGCACCAAAGAAACGGAGAGAAAAGAAACCAAAGCCGA
GGAGGAGCTGGATGCCGAAGTCCTGGAGGTGTTCCACCCGACGCATGAGTGGCAGGCCCT
TCAGCCAGGGCAGGCTGTCCCTGCAGGATCCCACGTACGGCTGAATCTTCAGACTGGGGA
AAGAGAGGCAAAACTCCAATATGAGGACAAGTTCCGAAATAATTTGAAAGGCAAAAGGCT
GGATATCAACACCAACACCTACACATCTCAGGATCTCAAGAGTGCACTGGCAAAATTCAA
GGAGGGGGCAGAGATGGAGAGTTCAAAGGAAGACAAGGCAAGGCAGGCTGAGGTAAAGCG
GCTCTTCCGCCCCATTGAGGAACTGAAGAAAGACTTTGATGAGCTGAATGTTGTCATTGA
GACTGACATGCAGATCATGGTACGGCTGATCAACAAGTTCAATAGTTCCAGCTCCAGTTT
GGAAGAGAAGATTGCTGCGCTCTTTGATCTTGAATATTATGTCCATCAGATGGACAATGC
GCAGGACCTGCTTTCCTTTGGTGGTCTTCAAGTGGTGATCAATGGGCTGAACAGCACAGA
GCCCCTCGTGAAGGAGTATGCTGCGTTTGTGCTGGGCGCTGCCTTTTCCAGCAACCCCAA
GGTCCAGGTGGAGGCCATCGAAGGGGGAGCCCTGCAGAAGCTGCTGGTCATCCTGGCCAC
GGAGCAGCCGCTCACTGCAAAGAAGAAGGTCCTGTTTGCACTGTGCTCCCTGCTGCGCCA
CTTCCCCTATGCCCAGCGGCAGTTCCTGAAGCTCGGGGGGCTGCAGGTCCTGAGGACCCT
GGTGCAGGAGAAGGGCACGGAGGTGCTCGCCGTGCGCGTGGTCACACTGCTCTACGACCT
GGTCACGGAGAAGATGTTCGCCGAGGAGGAGGCTGAGCTGACCCAGGAGATGTCCCCAGA
GAAGCTGCAGCAGTATCGCCAGGTACACCTCCTGCCAGGCCTGTGGGAACAGGGCTGGTG
CGAGATCACGGCCCACCTCCTGGCGCTGCCCGAGCATGATGCCCGTGAGAAGGTGCTGCA
GACACTGGGCGTCCTCCTGACCACCTGCCGGGACCGCTACCGTCAGGACCCCCAGCTCGG
CAGGACACTGGCCAGCCTGCAGGCTGAGTACCAGGTGCTGGCCAGCCTGGAGCTGCAGGA
TGGTGAGGACGAGGGCTACTTCCAGGAGCTGCTGGGCTCTGTCAACAGCTTGCTGAAGGA
GCTGAGA<u>**TGA**</u>GGCCCCACACCAGGACTGGACTGGGATGCCGCTAGTGAGGCTGAGGGGTG
CCAGCGTGGGTGGGCTTCTCAGGCAGGAGGACATCTTGGCAGTGCTGGCTTGGCCATTAA
ATGGAAACCTGAAGGCCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 162

MAPQSLPSSRMAPLGMLLGLLMAACFTFCLSHQNLKEFALTNPEKSSTKETERKETKAEE
ELDAEVLEVFHPTHEWQALQPGQAVPAGSHVRLNLQTGEREAKLQYEDKFRNNLKGKRLD
INTNTYTSQDLKSALAKFKEGAEMESSKEDKARQAEVKRLFRPIEELKKDFDELNVVIET
DMQIMVRLINKFNSSSSSLEEKIAALFDLEYYVHQMDNAQDLLSFGGLQVVINGLNSTEP
LVKEYAAFVLGAAFSSNPKVQVEAIEGGALQKLLVILATEQPLTAKKKVLFALCSLLRHF
PYAQRQFLKLGGLQVLRTLVQEKGTEVLAVRVVTLLYDLVTEKMFAEEEAELTQEMSPEK
LQQYRQVHLLPGLWEQGWCEITAHLLALPEHDAREKVLQTLGVLLTTCRDRYRQDPQLGR
TLASLQAEYQVLASLELQDGEDEGYFQELLGSVNSLLKELR

Important features:
Signal peptide:
amino acids 1-29

Hypothetical YJL126w/YLR351c/yhcX family protein:
amino acids 364-373

N-glycosylation site:
amino acids 193-197, 236-240

N-myristoylation site:
amino acids 15-21, 19-25, 234-240, 251-257, 402-408, 451-457

Homologous region SLS1 protein:
amino acids 68-340

FIGURE 163

CAGAGAGGAGGCTTTGGGAATTGTCCAGCAGAAACAGAGAAGTCTGAGGTGGTGTCAAGA
CAAAAG**ATG**CTTCAGCTTTGGAAACTTGTTCTCCTGTGCGGCGTGCTCACTGGGACCTCA
GAGTCTCTTCTTGACAATCTTGGCAATGACCTAAGCAATGTCGTGGATAAGCTGGAACCT
GTTCTTCACGAGGGACTTGAGACAGTTGACAATACTCTTAAAGGCATCCTTGAGAAACTG
AAGGTCGACCTAGGAGTGCTTCAGAAATCCAGTGCTTGGCAACTGGCCAAGCAGAAGGCC
CAGGAAGCTGAGAAATTGCTGAACAATGTCATTTCTAAGCTGCTTCCAACTAACACGGAC
ATTTTTGGGTTGAAAATCAGCAACTCCCTCATCCTGGATGTCAAAGCTGAACCGATCGAT
GATGGCAAAGGCCTTAACCTGAGCTTCCCTGTCACCGCGAATGTCACTGTGGCCGGGCCC
ATCATTGGCCAGATTATCAACCTGAAAGCCTCCTTGGACCTCCTGACCGCAGTCACAATT
GAAACTGATCCCCAGACACACCAGCCTGTTGCCGTCCTGGGAGAATGCGCCAGTGACCCA
ACCAGCATCTCACTTTCCTTGCTGGACAAACACAGCCAAATCATCAACAAGTTCGTGAAT
AGCGTGATCAACACGCTGAAAAGCACTGTATCCTCCCTGCTGCAGAAGGAGATATGTCCA
CTGATCCGCATCTTCATCCACTCCCTGGATGTGAATGTCATTCAGCAGGTCGTCGATAAT
CCTCAGCACAAAACCCAGCTGCAAACCCTCATC**TGA**AGAGGACGAATGAGGAGGACCACT
GTGGTGCATGCTGATTGGTTCCCAGTGGCTTGCCCCACCCCCTTATAGCATCTCCCTCCA
GGAAGCTGCTGCCACCACCTAACCAGCGTGAAAGCCTGAGTCCCACCAGAAGGACCTTCC
CAGATACCCCTTCTCCTCACAGTCAGAACAGCAGCCTCTACACATGTTGTCCTGCCCCTG
GCAATAAAGGCCCATTTCTGCACCCTTAA

FIGURE 164

MLQLWKLVLLCGVLTGTSESLLDNLGNDLSNVVDKLEPVLHEGLETVDNTLKGILEKLKV
DLGVLQKSSAWQLAKQKAQEAEKLLNNVISKLLPTNTDIFGLKISNSLILDVKAEPIDDG
KGLNLSFPVTANVTVAGPIIGQIINLKASLDLLTAVTIETDPQTHQPVAVLGECASDPTS
ISLSLLDKHSQIINKFVNSVINTLKSTVSSLLQKEICPLIRIFIHSLDVNVIQQVVDNPQ
HKTQLQTLI

Important features:

Signal peptide:
1-15

Transmembrane domain:
none

N-glycosylation site:
124-128, 132-136

N-myristoylation site:
12-18, 16-22, 26-32, 101-107, 122-128, 141-147

Leucine zipper pattern:
44-66

FIGURE 165

GCAGTCAGAGACTTCCCCTGCCCCTCGCTGGGAAAGAACATTAGGAATGCCTTTTAGTGC
CTTGCTTCCTGAACTAGCTCACAGTAGCCCGGCGGCCCAGGGCAATCCGACCACATTTCA
CTCTCACCGCTGTAGGAATCCAG<u>ATG</u>CAGGCCAAGTACAGCAGCACGAGGGACATGCTGG
ATGATGATGGGGACACCACCATGAGCCTGCATTCTCAAGCCTCTGCCACAACTCGGCATC
CAGAGCCCCGGCGCACAGAGCACAGGGCTCCCTCTTCAACGTGGCGACCAGTGGCCCTGA
CCCTGCTGACTTTGTGCTTGGTGCTGCTGATAGGGCTGGCAGCCCTGGGGCTTTTGTTTT
TTCAGTACTACCAGCTCTCCAATACTGGTCAAGACACCATTTCTCAAATGGAAGAAAGAT
TAGGAAATACGTCCCAAGAGTTGCAATCTCTTCAAGTCCAGAATATAAAGCTTGCAGGAA
GTCTGCAGCATGTGGCTGAAAAACTCTGTCGTGAGCTGTATAACAAAGCTGGAGCACACA
GGTGCAGCCCTTGTACAGAACAATGGAAATGGCATGGAGACAATTGCTACCAGTTCTATA
AAGACAGCAAAAGTTGGGAGGACTGTAAATATTTCTGCCTTAGTGAAAACTCTACCATGC
TGAAGATAAACAAACAAGAAGACCTGGAATTTGCCGCGTCTCAGAGCTACTCTGAGTTTT
TCTACTCTTATTGGACAGGGCTTTTGCGCCCTGACAGTGGCAAGGCCTGGCTGTGGATGG
ATGGAACCCCTTTCACTTCTGAACTGTTCCATATTATAATAGATGTCACCAGCCCAAGAA
GCAGAGACTGTGTGGCCATCCTCAATGGGATGATCTTCTCAAAGGACTGCAAAGAATTGA
AGCGTTGTGTCTGTGAGAGAAGGGCAGGAATGGTGAAGCCAGAGAGCCTCCATGTCCCCC
CTGAAACATTAGGCGAAGGTGAC<u>TGA</u>TTCGCCCTCTGCAACTACAAATAGCAGAGTGAGC
CAGGCGGTGCCAAAGCAAGGGCTAGTTGAGACATTGGGAAATGGAACATAATCAGGAAAG
ACTATCTCTCTGACTAGTACAAAATGGGTTCTCGTGTTTCCTGTTCAGGATCACCAGCAT
TTCTGAGCTTGGGTTTATGCACGTATTTAACAGTCACAAGAAGTCTTATTTACATGCCAC
CAACCAACCTCAGAAACCCATAATGTCATCTGCCTTCTTGGCTTAGAGATAACTTTTAGC
TCTCTTTCTTCTCAATGTCTAATATCACCTCCCTGTTTTCATGTCTTCCTTACACTTGGT
GGAATAAGAAACTTTTTGAAGTAGAGGAAATACATTGAGGTAACATCCTTTTCTCTGACA
GTCAAGTAGTCCATCAGAAATTGGCAGTCACTTCCCAGATTGTACCAGCAAATACACAAG
GAATTCTTTTTGTTTGTTTCAGTTCATACTAGTCCCTTCCCAATCCATCAGTAAAGACCC
CATCTGCCTTGTCCATGCCGTTTCCCAACAGGGATGTCACTTGATATGAGAATCTCAAAT
CTCAATGCCTTATAAGCATTCCTTCCTGTGTCCATTAAGACTCTGATAATTGTCTCCCCT
CCATAGGAATTTCTCCCAGGAAAGAAATATATCCCCATCTCCGTTTCATATCAGAACTAC
CGTCCCCGATATTCCCTTCAGAGAGATTAAAGACCAGAAAAAAGTGAGCCTCTTCATCTG
CACCTGTAATAGTTTCAGTTCCTATTTTCTTCCATTGACCCATATTTATACCTTTCAGGT
ACTGAAGATTTAATAATAATAAATGTAAATACTGTGAAAAA

FIGURE 166

MQAKYSSTRDMLDDDGDTTMSLHSQASATTRHPEPRRTEHRAPSSTWRPVALTLLTLCLV
LLIGLAALGLLFFQYYQLSNTGQDTISQMEERLGNTSQELQSLQVQNIKLAGSLQHVAEK
LCRELYNKAGAHRCSPCTEQWKWHGDNCYQFYKDSKSWEDCKYFCLSENSTMLKINKQED
LEFAASQSYSEFFYSYWTGLLRPDSGKAWLWMDGTPFTSELFHIIIDVTSPRSRDCVAIL
NGMIFSKDCKELKRCVCERRAGMVKPESLHVPPETLGEGD

FIGURE 167

GCGACGGGCAGGACGCCCCGTTCGCCTAGCGCGTGCTCAGGAGTTGGTGTCCTGCCTGCG
CTCAGGATGAGGGGGAATCTGGCCCTGGTGGGCGTTCTAATCAGCCTGGCCTTCCTGTCA
CTGCTGCCATCTGGACATCCTCAGCCGGCTGGCGATGACGCCTGCTCTGTGCAGATCCTC
GTCCCTGGCCTCAAAGGGGATGCGGGAGAGAAGGGAGACAAAGGCGCCCCCGGACGGCCT
GGAAGAGTCGGCCCCACGGGAGAAAAAGGAGACATGGGGGACAAAGGACAGAAAGGCAGT
GTGGGTCGTCATGGAAAAATTGGTCCCATTGGCTCTAAAGGTGAGAAAGGAGATTCCGGT
GACATAGGACCCCCTGGTCCTAATGGAGAACCAGGCCTCCCATGTGAGTGCAGCCAGCTG
CGCAAGGCCATCGGGGAGATGGACAACCAGGTCTCTCAGCTGACCAGCGAGCTCAAGTTC
ATCAAGAATGCTGTCGCCGGTGTGCGCGAGACGGAGAGCAAGATCTACCTGCTGGTGAAG
GAGGAGAAGCGCTACGCGGACGCCCAGCTGTCCTGCCAGGGCCGCGGGGGCACGCTGAGC
ATGCCCAAGGACGAGGCTGCCAATGGCCTGATGGCCGCATACCTGGCGCAAGCCGGCCTG
GCCCGTGTCTTCATCGGCATCAACGACCTGGAGAAGGAGGGCGCCTTCGTGTACTCTGAC
CACTCCCCCATGCGGACCTTCAACAAGTGGCGCAGCGGTGAGCCCAACAATGCCTACGAC
GAGGAGGACTGCGTGGAGATGGTGGCCTCGGGCGGCTGGAACGACGTGGCCTGCCACACC
ACCATGTACTTCATGTGTGAGTTTGACAAGGAGAACATGTGAGCCTCAGGCTGGGGCTGC
CCATTGGGGGCCCCACATGTCCCTGCAGGGTTGGCAGGGACAGAGCCCAGACCATGGTGC
CAGCCAGGGAGCTGTCCCTCTGTGAAGGGTGGAGGCTCACTGAGTAGAGGGCTGTTGTCT
AAACTGAGAAAATGGCCTATGCTTAAGAGGAAAATGAAAGTGTTCCTGGGGTGCTGTCTC
TGAAGAAGCAGAGTTTCATTACCTGTATTGTAGCCCCAATGTCATTATGTAATTATTACC
CAGAATTGCTCTTCCATAAAGCTTGTGCCTTTGTCCAAGCTATACAATAAAATCTTTAAG
TAGTGCAGTAGTTAAGTCCAAAAAAAAAAAAAAAAAA

FIGURE 168

MRGNLALVGVLISLAFLSLLPSGHPQPAGDDACSVQILVPGLKGDAGEKGDKGAPGRPGR
VGPTGEKGDMGDKGQKGSVGRHGKIGPIGSKGEKGDSGDIGPPGPNGEPGLPCECSQLRK
AIGEMDNQVSQLTSELKFIKNAVAGVRETESKIYLLVKEEKRYADAQLSCQGRGGTLSMP
KDEAANGLMAAYLAQAGLARVFIGINDLEKEGAFVYSDHSPMRTFNKWRSGEPNNAYDEE
DCVEMVASGGWNDVACHTTMYFMCEFDKENM

FIGURE 169

AGTGACTGCAGCCTTCCTAGATCCCCTCCACTCGGTTTCTCTCTTTGCAGGAGCACCGGC
AGCACCAGTGTGTGAGGGGAGCAGGCAGCGGTCCTAGCCAGTTCCTTGATCCTGCCAGAC
CACCCAGCCCCCGGCACAGAGCTGCTCCACAGGCACC**ATG**AGGATCATGCTGCTATTCAC
AGCCATCCTGGCCTTCAGCCTAGCTCAGAGCTTTGGGGCTGTCTGTAAGGAGCCACAGGA
GGAGGTGGTTCCTGGCGGGGGCCGCAGCAAGAGGGATCCAGATCTCTACCAGCTGCTCCA
GAGACTCTTCAAAAGCCACTCATCTCTGGAGGGATTGCTCAAAGCCCTGAGCCAGGCTAG
CACAGATCCTAAGGAATCAACATCTCCCGAGAAACGTGACATGCATGACTTCTTTGTGGG
ACTTATGGGCAAGAGGAGCGTCCAGCCAGAGGGAAAGACAGGACCTTTCTTACCTTCAGT
GAGGGTTCCTCGGCCCCTTCATCCCAATCAGCTTGGATCCACAGGAAAGTCTTCCCTGGG
AACAGAGGAGCAGAGACCTTTA**TAA**GACTCTCCTACGGATGTGAATCAAGAGAACGTCCC
CAGCTTTGGCATCCTCAAGTATCCCCCGAGAGCAGAATAGGTACTCCACTTCCGGACTCC
TGGACTGCATTAGGAAGACCTCTTTCCCTGTCCCAATCCCCAGGTGCGCACGCTCCTGTT
ACCCTTTCTCTTCCCTGTTCTTGTAACATTCTTGTGCTTTGACTCCTTCTCCATCTTTTC
TACCTGACCCTGGTGTGGAAACTGCATAGTGAATATCCCCAACCCCAATGGGCATTGACT
GTAGAATACCCTAGAGTTCCTGTAGTGTCCTACATTAAAAATATAATGTCTCTCTCTATT
CCTCAACAATAAAGGATTTTGCATATGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAA

FIGURE 170

MRIMLLFTAILAFSLAQSFGAVCKEPQEEVVPGGGRSKRDPDLYQLLQRLFKSHSSLEGL
LKALSQASTDPKESTSPEKRDMHDFFVGLMGKRSVQPEGKTGPFLPSVRVPRPLHPNQLG
STGKSSLGTEEQRPL

Important features:
Signal peptide:
amino acids 1-18

Tyrosine kinase phosphorylation site:
amino acids 36-45

N-myristoylation site:
amino acids 33-39, 59-65

Amidation site:
amino acids 90-94

Leucine zipper pattern:
amino acids 43-65

Tachykinin family signature:
amino acids 86-92

FIGURE 171

TGGCCTCCCCAGCTTGCCAGGCACAAGGCTGAGCGGGAGGAAGCGAGAGGCATCTAAGCA
GGCAGTGTTTTGCCTTCACCCCAAGTGACC<u>ATG</u>AGAGGTGCCACGCGAGTCTCAATCATG
CTCCTCCTAGTAACTGTGTCTGACTGTGCTGTGATCACAGGGGCCTGTGAGCGGGATGTC
CAGTGTGGGGCAGGCACCTGCTGTGCCATCAGCCTGTGGCTTCGAGGGCTGCGGATGTGC
ACCCCGCTGGGGCGGGAAGGCGAGGAGTGCCACCCCGGCAGCCACAAGGTCCCCTTCTTC
AGGAAACGCAAGCACCACACCTGTCCTTGCTTGCCCAACCTGCTGTGCTCCAGGTTCCCG
GACGGCAGGTACCGCTGCTCCATGGACTTGAAGAACATCAATTTT<u>TAG</u>GCGCTTGCCTGG
TCTCAGGATACCCACCATCCTTTTCCTGAGCACAGCCTGGATTTTTATTTCTGCCATGAA
ACCCAGCTCCCATGACTCTCCCAGTCCCTACACTGACTACCCTGATCTCTCTTGTCTAGT
ACGCACATATGCACACAGGCAGACATACCTCCCATCATGACATGGTCCCCAGGCTGGCCT
GAGGATGTCACAGCTTGAGGCTGTGGTGTGAAAGGTGGCCAGCCTGGTTCTCTTCCCTGC
TCAGGCTGCCAGAGAGGTGGTAAATGGCAGAAAGGACATTCCCCCTCCCCTCCCCAGGTG
ACCTGCTCTCTTTCCTGGGCCCTGCCCCTCTCCCCACATGTATCCCTCGGTCTGAATTAG
ACATTCCTGGGCACAGGCTCTTGGGTGCATTGCTCAGAGTCCCAGGTCCTGGCCTGACCC
TCAGGCCCTTCACGTGAGGTCTGTGAGGACCAATTTGTGGGTAGTTCATCTTCCCTCGAT
TGGTTAACTCCTTAGTTTCAGACCACAGACTCAAGATTGGCTCTTCCCAGAGGGCAGCAG
ACAGTCACCCCAAGGCAGGTGTAGGGAGCCCAGGGAGGCCAATCAGCCCCCTGAAGACTC
TGGTCCCAGTCAGCCTGTGGCTTGTGGCCTGTGACCTGTGACCTTCTGCCAGAATTGTCA
TGCCTCTGAGGCCCCCTCTTACCACACTTTACCAGTTAACCACTGAAGCCCCCAATTCCC
ACAGCTTTTCCATTAAAATGCAAATGGTGGTGGTTCAATCTAATCTGATATTGACATATT
AGAAGGCAATTAGGGTGTTTCCTTAAACAACTCCTTTCCAAGGATCAGCCCTGAGAGCAG
GTTGGTGACTTTGAGGAGGGCAGTCCTCTGTCCAGATTGGGGTGGGAGCAAGGGACAGGG
AGCAGGGCAGGGGCTGAAAGGGGCACTGATTCAGACCAGGGAGGCAACTACACACCAACA
TGCTGGCTTTAGAATAAAAGCACCAACTGAAAAAA

FIGURE 172

MRGATRVSIMLLLVTVSDCAVITGACERDVQCGAGTCCAISLWLRGLRMCTPLGREGEEC
HPGSHKVPFFRKRKHHTCPCLPNLLCSRFPDGRYRCSMDLKNINF

Signal peptide:
amino acids 1-19

Tyrosine kinase phosphorylation site:
amino acids 88-95

N-myristoylation sites:
amino acids 33-39, 35-41, 46-52

FIGURE 173

AGCGCCCGGGCGTCGGGGCGGTAAAAGGCCGGCAGAAGGGAGGCACTTGAGAA**ATG**TCTT
TCCTCCAGGACCCAAGTTTCTTCACCATGGGGATGTGGTCCATTGGTGCAGGAGCCCTGG
GGGCTGCTGCCTTGGCATTGCTGCTTGCCAACACAGACGTGTTTCTGTCCAAGCCCCAGA
AAGCGGCCCTGGAGTACCTGGAGGATATAGACCTGAAAACACTGGAGAAGGAACCAAGGA
CTTTCAAAGCAAAGGAGCTATGGGAAAAAAATGGAGCTGTGATTATGGCCGTGCGGAGGC
CAGGCTGTTTCCTCTGTCGAGAGGAAGCTGCGGATCTGTCCTCCCTGAAAAGCATGTTGG
ACCAGCTGGGCGTCCCCCTCTATGCAGTGGTAAAGGAGCACATCAGGACTGAAGTGAAGG
ATTTCCAGCCTTATTTCAAAGGAGAAATCTTCCTGGATGAAAAGAAAAAGTTCTATGGTC
CACAAAGGCGGAAGATGATGTTTATGGGATTTATCCGTCTGGGAGTGTGGTACAACTTCT
TCCGAGCCTGGAACGGAGGCTTCTCTGGAAACCTGGAAGGAGAAGGCTTCATCCTTGGGG
GAGTTTTCGTGGTGGGATCAGGAAAGCAGGGCATTCTTCTTGAGCACCGAGAAAAAGAAT
TTGGAGACAAAGTAAACCTACTTTCTGTTCTGGAAGCTGCTAAGATGATCAAACCACAGA
CTTTGGCCTCAGAGAAAAAA**TGA**TTGTGTGAAACTGCCCAGCTCAGGGATAACCAGGGAC
ATTCACCTGTGTTCATGGGATGTATTGTTTCCACTCGTGTCCCTAAGGAGTGAGAAACCC
ATTTATACTCTACTCTCAGTATGGATTATTAATGTATTTTAATATTCTGTTTAGGCCCAC
TAAGGCAAAATAGCCCCAAAACAAGACTGACAAAAATCTGAAAAACTAATGAGGATTATT
AAGCTAAAACCTGGGAAATAGGAGGCTTAAAATTGACTGCCAGGCTGGGTGCAGTGGCTC
ACACCTGTAATCCCAGCACTTTGGGAGGCCAAGGTGAGCAAGTCACTTGAGGTCGGGAGT
TCGAGACCAGCCTGAGCAACATGGCGAAACCCCGTCTCTACTAAAAATACAAAAATCACC
CGGGTGTGGTGGCAGGCACCTGTAGTCCCAGCTACCCGGGAGGCTGAGGCAGGAGAATCA
CTTGAACCTGGGAGGTGGAGGTTGCGGTGAGCTGAGATCACACCACTGTATTCCAGCCTG
GGTGACTGAGACTCTAACTAA

FIGURE 174

MSFLQDPSFFTMGMWSIGAGALGAAALALLLANTDVFLSKPQKAALEYLEDIDLKTLEKE
PRTFKAKELWEKNGAVIMAVRRPGCFLCREEAADLSSLKSMLDQLGVPLYAVVKEHIRTE
VKDFQPYFKGEIFLDEKKKFYGPQRRKMMFMGFIRLGVWYNFFRAWNGGFSGNLEGEGFI
LGGVFVVGSGKQGILLEHREKEFGDKVNLLSVLEAAKMIKPQTLASEKK

FIGURE 175

GACAGTGGAGGGCAGTGGAGAGGACCGCGCTGTCCTGCTGTCACCAAGAGCTGGAGACAC
CATCTCCCACCGAGAGTC<u>ATG</u>GCCCCATTGGCCCTGCACCTCCTCGTCCTCGTCCCCATC
CTCCTCAGCCTGGTGGCCTCCCAGGACTGGAAGGCTGAACGCAGCCAAGACCCCTTCGAG
AAATGCATGCAGGATCCTGACTATGAGCAGCTGCTCAAGGTGGTGACCTGGGGGCTCAAT
CGGACCCTGAAGCCCCAGAGGGTGATTGTGGTTGGCGCTGGTGTGGCCGGGCTGGTGGCC
GCCAAGGTGCTCAGCGATGCTGGACACAAGGTCACCATCCTGGAGGCAGATAACAGGATC
GGGGGCCGCATCTTCACCTACCGGGACCAGAACACGGGCTGGATTGGGGAGCTGGGAGCC
ATGCGCATGCCCAGCTCTCACAGGATCCTCCACAAGCTCTGCCAGGGCCTGGGGCTCAAC
CTGACCAAGTTCACCCAGTACGACAAGAACACGTGGACGGAGGTGCACGAAGTGAAGCTG
CGCAACTATGTGGTGGAGAAGGTGCCCGAGAAGCTGGGCTACGCCTTGCGTCCCCAGGAA
AAGGGCCACTCGCCCGAAGACATCTACCAGATGGCTCTCAACCAGGCCCTCAAAGACCTC
AAGGCACTGGGCTGCAGAAAGGCGATGAAGAAGTTTGAAAGGCACACGCTCTTGGAATAT
CTTCTCGGGGAGGGGAACCTGAGCCGGCCGGCCGTGCAGCTTCTGGGAGACGTGATGTCC
GAGGATGGCTTCTTCTATCTCAGCTTCGCCGAGGCCCTCCGGGCCCACAGCTGCCTCAGC
GACAGACTCCAGTACAGCCGCATCGTGGGTGGCTGGGACCTGCTGCCGCGCGCGCTGCTG
AGCTCGCTGTCCGGGCTTGTGCTGTTGAACGCGCCCGTGGTGGCGATGACCCAGGGACCG
CACGATGTGCACGTGCAGATCGAGACCTCTCCCCCGGCGCGGAATCTGAAGGTGCTGAAG
GCCGACGTGGTGCTGCTGACGGCGAGCGGACCGGCGGTGAAGCGCATCACCTTCTCGCCG
CCGCTGCCCCGCCACATGCAGGAGGCGCTGCGGAGGCTGCACTACGTGCCGGCCACCAAG
GTGTTCCTAAGCTTCCGCAGGCCCTTCTGGCGCGAGGAGCACATTGAAGGCGGCCACTCA
AACACCGATCGCCCGTCGCGCATGATTTTCTACCCGCCGCCGCGCGAGGGCGCGCTGCTG
CTGGCCTCGTACACGTGGTCGGACGCGGCGGCAGCGTTCGCCGGCTTGAGCCGGGAAGAG
GCGTTGCGCTTGGCGCTCGACGACGTGGCGGCATTGCACGGGCCTGTCGTGCGCCAGCTC
TGGGACGGCACCGGCGTCGTCAAGCGTTGGGCGGAGGACCAGCACAGCCAGGGTGGCTTT
GTGGTACAGCCGCCGGCGCTCTGGCAAACCGAAAAGGATGACTGGACGGTCCCTTATGGC
CGCATCTACTTTGCCGGCGAGCACACCGCCTACCCGCACGGCTGGGTGGAGACGGCGGTC
AAGTCGGCGCTGCGCGCCGCCATCAAGATCAACAGCCGGAAGGGGCCTGCATCGGACACG
GCCAGCCCCGAGGGGCACGCATCTGACATGGAGGGGCAGGGGCATGTGCATGGGGTGGCC
AGCAGCCCCTCGCATGACCTGGCAAAGGAAGAAGGCAGCCACCCTCCAGTCCAAGGCCAG
TTATCTCTCCAAAACACGACCCACACGAGGACCTCGCAT<u>TAA</u>AGTATTTTCGGAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 176

MAPLALHLLVLVPILLSLVASQDWKAERSQDPFEKCMQDPDYEQLLKVVTWGLNRTLKPQ
RVIVVGAGVAGLVAAKVLSDAGHKVTILEADNRIGGRIFTYRDQNTGWIGELGAMRMPSS
HRILHKLCQGLGLNLTKFTQYDKNTWTEVHEVKLRNYVVEKVPEKLGYALRPQEKGHSPE
DIYQMALNQALKDLKALGCRKAMKKFERHTLLEYLLGEGNLSRPAVQLLGDVMSEDGFFY
LSFAEALRAHSCLSDRLQYSRIVGGWDLLPRALLSSLSGLVLLNAPVVAMTQGPHDVHVQ
IETSPPARNLKVLKADVVLLTASGPAVKRITFSPPLPRHMQEALRRLHYVPATKVFLSFR
RPFWREEHIEGGHSNTDRPSRMIFYPPPREGALLLASYTWSDAAAAFAGLSREEALRLAL
DDVAALHGPVVRQLWDGTGVVKRWAEDQHSQGGFVVQPPALWQTEKDDWTVPYGRIYFAG
EHTAYPHGWVETAVKSALRAAIKINSRKGPASDTASPEGHASDMEGQGHVHGVASSPSHD
LAKEEGSHPPVQGQLSLQNTTHTRTSH

Signal peptide:
amino acids 1-21

FIGURE 177

CCGGGGAGGGGAGGGCCCGTCCCGCCCCTCCCCGTCTCTCCCCGCCCCTCCCCGTCCCTC
CCGCCGAAGCTCCGTCCCGCCCGCGGGCCGGCTCCGCCCTCACCTCCCGGCCGCGGCTGC
CCTCTGCCCGGGTTGTCCAAG**ATG**GAGGGCGCTCCACCGGGGTCGCTCGCCCTCCGGCTC
CTGCTGTTCGTGGCGCTACCCGCCTCCGGCTGGCTGACGACGGGCGCCCCCGAGCCGCCG
CCGCTGTCCGGAGCCCCACAGGACGGCATCAGAATTAATGTAACTACACTGAAAGATGAT
GGGGACATATCTAAACAGCAGGTTGTTCTTAACATAACCTATGAGAGTGGACAGGTGTAT
GTAAATGACTTACCTGTAAATAGTGGTGTAACCCGAATAAGCTGTCAGACTTTGATAGTG
AAGAATGAAAATCTTGAAAATTTGGAGGAAAAAGAATATTTTGGAATTGTCAGTGTAAGG
ATTTTAGTTCATGAGTGGCCTATGACATCTGGTTCCAGTTTGCAACTAATTGTCATTCAA
GAAGAGGTAGTAGAGATTGATGGAAAACAAGTTCAGCAAAAGGATGTCACTGAAATTGAT
ATTTTAGTTAAGAACCGGGGAGTACTCAGACATTCAAACTATACCCTCCCTTTGGAAGAA
AGCATGCTCTACTCTATTTCTCGAGACAGTGACATTTTATTTACCCTTCCTAACCTCTCC
AAAAAAGAAAGTGTTAGTTCACTGCAAACCACTAGCCAGTATCTTATCAGGAATGTGGAA
ACCACTGTAGATGAAGATGTTTTACCTGGCAAGTTACCTGAAACTCCTCTCAGAGCAGAG
CCGCCATCTTCATATAAGGTAATGTGTCAGTGGATGGAAAAGTTTAGAAAAGATCTGTGT
AGGTTCTGGAGCAACGTTTTCCCAGTATTCTTTCAGTTTT**TGA**ACATCATGGTGGTTGGA
ATTACAGGAGCAGCTGTGGTAATAACCATCTTAAAGGTGTTTTTCCCAGTTTCTGAATAC
AAAGGAATTCTTCAGTTGGATAAAGTGGACGTCATACCTGTGACAGCTATCAACTTATAT
CCAGATGGTCCAGAGAAAAGAGCTGAAAACCTTGAAGATAAAACATGTATTTAAAACGCC
ATCTCATATCATGGACTCCGAAGTAGCCTGTTGCCTCCAAATTTGCCACTTGAATATAAT
TTTCTTTAAATCGTT

FIGURE 178

MEGAPPGSLALRLLLFVALPASGWLTTGAPEPPPLSGAPQDGIRINVTTLKDDGDISKQQ
VVLNITYESGQVYVNDLPVNSGVTRISCQTLIVKNENLENLEEKEYFGIVSVRILVHEWP
MTSGSSLQLIVIQEEVVEIDGKQVQQKDVTEIDILVKNRGVLRHSNYTLPLEESMLYSIS
RDSDILFTLPNLSKKESVSSLQTTSQYLIRNVETTVDEDVLPGKLPETPLRAEPPSSYKV
MCQWMEKFRKDLCRFWSNVFPVFFQFLNIMVVGITGAAVVITILKVFFPVSEYKGILQLD
KVDVIPVTAINLYPDGPEKRAENLEDKTCI

Signal peptide:
1-23

Transmembrane domain:
266-284

Leucine zipper pattern:
155-177

N-glycosylation site:
46-50, 64-68, 166-170, 191-195

Motif name: N-myristoylation site:
3-9, 42-48, 273-279

FIGURE 179

CTCCTTAGGTGGAAACCCTGGGAGTAGAGTACTGACAGCAAAGACCGGGAAAGACCATAC
GTCCCCGGGCAGGGGTGACAACAGGTGTCATCTTTTTGATCTCGTGTGTGGCTGCCTTCC
TATTTCAAGGAAAGACGCCAAGGTAATTTTGACCCAGAGGAGCAATGATGTAGCCACCTC
CTAACCTTCCCTTCTTGAACCCCCAGTTATGCCAGGATTTACTAGAGAGTGTCAACTCAA
CCAGCAAGCGGCTCCTTCGGCTTAACTTGTGGTTGGAGGAGAGAACCTTTGTGGGGCTGC
GTTCTCTTAGCAGTGCTCAGAAGTGACTTGCCTGAGGGTGGACCAGAAGAAAGGAAAGGT
CCCCTCTTGCTGTTGGCTGCACATCAGGAAGGCTGTGATGGGAATGAAGGTGAAAACTTG
GAGATTTCACTTCAGTCATTGCTTCTGCCTGCAAGATCATCCTTTAAAAGTAGAGAAGCT
GCTCTGTGTGGTGGTTAACTCCAAGAGGCAGAACTCGTTCTAGAAGGAAATGGATGCAAG
CAGCTCCGGGGGCCCCAAACGCATGCTTCCTGTGGTCTAGCCCAGGGAAGCCCTTCCGTG
GGGGCCCCGGCTTTGAGGATGCCACCGGTTCTGGACGCATGGCTGATTCCTGA<u>ATG</u>ATG
ATGGTTCGCCGGGGGCTGCTTGCGTGGATTTCCCGGGTGGTGGTTTTGCTGGTGCTCCTC
TGCTGTGCTATCTCTGTCCTGTACATGTTGGCCTGCACCCCAAAAGGTGACGAGGAGCAG
CTGGCACTGCCCAGGGCCAACAGCCCCACGGGGAAGGAGGGGTACCAGGCCGTCCTTCAG
GAGTGGGAGGAGCAGCACCGCAACTACGTGAGCAGCCTGAAGCGGCAGATCGCACAGCTC
AAGGAGGAGCTGCAGGAGAGGAGTGAGCAGCTCAGGAATGGGCAGTACCAAGCCAGCGAT
GCTGCTGGCCTGGGTCTGGACAGGAGCCCCCCAGAGAAAACCCAGGCCGACCTCCTGGCC
TTCCTGCACTCGCAGGTGGACAAGGCAGAGGTGAATGCTGGCGTCAAGCTGGCCACAGAG
TATGCAGCAGTGCCTTTCGATAGCTTTACTCTACAGAAGGTGTACCAGCTGGAGACTGGC
CTTACCCGCCACCCCGAGGAGAAGCCTGTGAGGAAGGACAAGCGGGATGAGTTGGTGGAA
GCCATTGAATCAGCCTTGGAGACCCTGAACAATCCTGCAGAGAACAGCCCCAATCACCGT
CCTTACACGGCCTCTGATTTCATAGAAGGGATCTACCGAACAGAAAGGGACAAAGGGACA
TTGTATGAGCTCACCTTCAAAGGGGACCACAAACACGAATTCAAACGGCTCATCTTATTT
CGACCATTCAGCCCCATCATGAAAGTGAAAAATGAAAAGCTCAACATGGCCAACACGCTT
ATCAATGTTATCGTGCCTCTAGCAAAAAGGGTGGACAAGTTCCGGCAGTTCATGCAGAAT
TTCAGGGAGATGTGCATTGAGCAGGATGGGAGAGTCCATCTCACTGTTGTTTACTTTGGG
AAAGAAGAAATAAATGAAGTCAAAGGAATACTTGAAAACACTTCCAAAGCTGCCAACTTC
AGGAACTTTACCTTCATCCAGCTGAATGGAGAATTTTCTCGGGGAAAGGGACTTGATGTT
GGAGCCCGCTTCTGGAAGGGAAGCAACGTCCTTCTCTTTTTCTGTGATGTGGACATCTAC
TTCACATCTGAATTCCTCAATACGTGTAGGCTGAATACACAGCCAGGGAAGAAGGTATTT
TATCCAGTTCTTTTCAGTCAGTACAATCCTGGCATAATATACGGCCACCATGATGCAGTC
CCTCCCTTGGAACAGCAGCTGGTCATAAAGAAGGAAACTGGATTTTGGAGAGACTTTGGA
TTTGGGATGACGTGTCAGTATCGGTCAGACTTCATCAATATAGGTGGGTTTGATCTGGAC
ATCAAAGGCTGGGGCGGAGAGGATGTGCACCTTTATCGCAAGTATCTCCACAGCAACCTC
ATAGTGGTACGGACGCCTGTGCGAGGACTCTTCCACCTCTGGCATGAGAAGCGCTGCATG
GACGAGCTGACCCCCGAGCAGTACAAGATGTGCATGCAGTCCAAGGCCATGAACGAGGCA
TCCCACGGCCAGCTGGGCATGCTGGTGTTCAGGCACGAGATAGAGGCTCACCTTCGCAAA
CAGAAACAGAAGACAAGTAGCAAAAAAACA<u>TGA</u>ACTCCCAGAGAAGGATTGTGGGAGACA
CTTTTTCTTTCCTTTTGCAATTACTGAAAGTGGCTGCAACAGAGAAAAGACTTCCATAAA
GGACGACAAAAGAATTGGACTGATGGGTCAGAGATGAGAAAGCCTCCGATTTCTCTCTGT
TGGGCTTTTTACAACAGAAATCAAAATCTCCGCTTTGCCTGCAAAAGTAACCCAGTTGCA
CCCTGTGAAGTGTCTGACAAAGGCAGAATGCTTGTGAGATTATAAGCCTAATGGTGTGGA
GGTTTTGATGGTGTTTACAATACACTGAGACCTGTTGTTTTGTGTGCTCATTGAAATATT
CATGATTTAAGAGCAGTTTTGTAAAAAATTCATTAGCATGAAAGGCAAGCATATTTCTCC
TCATATGAATGAGCCTATCAGCAGGGCTCTAGTTTCTAGGAATGCTAAAATATCAGAAGG
CAGGAGAGGAGATAGGCTTATTATGATACTAGTGAGTACATTAAGTAAAATAAAATGGAC
CAGAAAAGAAAAGAAACCATAAATATCGTGTCATATTTTCCCCAAGATTAACCAAAAATA

ATCTGCTTATCTTTTTGGTTGTCCTTTTAACTGTCTCCGTTTTTTTCTTTTATTTAAAAA
TGCACTTTTTTTCCCTTGTGAGTTATAGTCTGCTTATTTAATTACCACTTTGCAAGCCTT
ACAAGAGAGCACAAGTTGGCCTACATTTTTATATTTTTTAAGAAGATACTTTGAGATGCA
TTATGAGAACTTTCAGTTCAAAGCATCAAATTGATGCCATATCCAAGGACATGCCAAATG
CTGATTCTGTCAGGCACTGAATGTCAGGCATTGAGACATAGGGAAGGAATGGTTTGTACT
AATACAGACGTACAGATACTTTCTCTGAAGAGTATTTTCGAAGAGGAGCAACTGAACACT
GGAGGAAAAGAAAATGACACTTTCTGCTTTACAGAAAAGGAAACTCATTCAGACTGGTGA
TATCGTGATGTACCTAAAAGTCAGAAACCACATTTTCTCCTCAGAAGTAGGGACCGCTTT
CTTACCTGTTTAAATAAACCAAAGTATACCGTGTGAACCAAACAATCTCTTTTCAAAACA
GGGTGCTCCTCCTGGCTTCTGGCTTCCATAAGAAGAAATGGAGAAAAATATATATATATA
TATATATATTGTGAAAGATCAATCCATCTGCCAGAATCTAGTGGGATGGAAGTTTTTGCT
ACATGTTATCCACCCCAGGCCAGGTGGAAGTAACTGAATTATTTTTTAAATTAAGCAGTT
CTACTCAATCACCAAGATGCTTCTGAAAATTGCATTTTATTACCATTTCAAACTATTTTT
TAAAAATAAATACAGTTAACATAGAGTGGTTTCTTCATTCATGTGAAAATTATTAGCCAG
CACCAGATGCATGAGCTAATTATCTCTTTGAGTCCTTGCTTCTGTTTGCTCACAGTAAAC
TCATTGTTTAAAAGCTTCAAGAACATTCAAGCTGTTGGTGTGTTAAAAAATGCATTGTAT
TGATTTGTACTGGTAGTTTATGAAATTTAATTAAAACACAGGCCATGAATGGAAGGTGGT
ATTGCACAGCTAATAAAATATGATTTGTGGATATGAA

FIGURE 180

MMMVRRGLLAWISRVVVLLVLLCCAISVLYMLACTPKGDEEQLALPRANSPTGKEGYQAV
LQEWEEQHRNYVSSLKRQIAQLKEELQERSEQLRNGQYQASDAAGLGLDRSPPEKTQADL
LAFLHSQVDKAEVNAGVKLATEYAAVPFDSFTLQKVYQLETGLTRHPEEKPVRKDKRDEL
VEAIESALETLNNPAENSPNHRPYTASDFIEGIYRTERDKGTLYELTFKGDHKHEFKRLI
LFRPFSPIMKVKNEKLNMANTLINVIVPLAKRVDKFRQFMQNFREMCIEQDGRVHLTVVY
FGKEEINEVKGILENTSKAANFRNFTFIQLNGEFSRGKGLDVGARFWKGSNVLLFFCDVD
IYFTSEFLNTCRLNTQPGKKVFYPVLFSQYNPGIIYGHHDAVPPLEQQLVIKKETGFWRD
FGFGMTCQYRSDFINIGGFDLDIKGWGGEDVHLYRKYLHSNLIVVRTPVRGLFHLWHEKR
CMDELTPEQYKMCMQSKAMNEASHGQLGMLVFRHEIEAHLRKQKQKTSSKKT

FIGURE 181

CGTCTCTGCGTTCGCC<u>ATG</u>CGTCCCGGGGCGCCAGGGCCACTCTGGCCTCTGCCCTGGGG
GGCCCTGGCTTGGGCCGTGGGCTTCGTGAGCTCCATGGGCTCGGGGAACCCCGCGCCCGG
TGGTGTTTGCTGGCTCCAGCAGGGCCAGGAGGCCACCTGCAGCCTGGTGCTCCAGACTGA
TGTCACCCGGGCCGAGTGCTGTGCCTCCGGCAACATTGACACCGCCTGGTCCAACCTCAC
CCACCCGGGGAACAAGATCAACCTCCTCGGCTTCTTGGGCCTTGTCCACTGCCTTCCCTG
CAAAGATTCGTGCGACGGCGTGGAGTGCGGCCCGGGCAAGGCGTGCCGCATGCTGGGGGG
CCGCCCGCGCTGCGAGTGCGCGCCCGACTGCTCGGGGCTCCCGGCGCGGCTGCAGGTCTG
CGGCTCAGACGGCGCCACCTACCGCGACGAGTGCGAGCTGCGCGCCGCGCGCTGCCGCGG
CCACCCGGACCTGAGCGTCATGTACCGGGGCCGCTGCCGCAAGTCCTGTGAGCACGTGGT
GTGCCCGCGGCCACAGTCGTGCGTCGTGGACCAGACGGGCAGCGCCCACTGCGTGGTGTG
TCGAGCGGCGCCCTGCCCTGTGCCCTCCAGCCCCGGCCAGGAGCTTTGCGGCAACAACAA
CGTCACCTACATCTCCTCGTGCCACATGCGCCAGGCCACCTGCTTCCTGGGCCGCTCCAT
CGGCGTGCGCCACGCGGGCAGCTGCGCAGGCACCCCTGAGGAGCCGCCAGGTGGTGAGTC
TGCAGAAGAGGAAGAGAACTTCGTG<u>TGA</u>GCCTGCAGGACAGGCCTGGGCCTGGTGCCCGA
GGCCCCCCATCATCCCCTGTTATTTATTGCCACAGCAGAGTCTAATTTATATGCCACGGA
CACTCCTTAGAGCCCGGATTCGGACCACTTGGGGATCCCAGAACCTCCCTGACGATATCC
TGGAAGGACTGAGGAAGGGAGGCCTGGGGGCCGGCTGGTGGGTGGGATAGACCTGCGTTC
CGGACACTGAGCGCCTGATTTAGGGCCCTTCTCTAGGATGCCCCAGCCCCTACCCTAAGA
CCTATTGCCGGGGAGGATTCCACACTTCCGCTCCTTTGGGGATAAACCTATTAATTATTG
CTACTATCAAGAGGGCTGGGCATTCTCTGCTGGTAATTCCTGAAGAGGCATGACTGCTTT
TCTCAGCCCCAAGCCTCTAGTCTGGGTGTGTACGGAGGGTCTAGCCTGGGTGTGTACGGA
GGGTCTAGCCTGGGTGAGTACGGAGGGTCTAGCCTGGGTGAGTACGGAGGGTCTAGCCTG
GGTGAGTACGGAGGGTCTAGCCTGGGTGTGTATGGAGGATCTAGCCTGGGTGAGTATGGA
GGGTCTAGCCTGGGTGAGTATGGAGGGTCTAGCCTGGGTGTGTATGGAGGGTCTAGCCTG
GGTGAGTATGGAGGGTCTAGCCTGGGTGTGTATGGAGGGTCTAGCCTGGGTGAGTATGGA
GGGTCTAGCCTGGGTGTGTACGGAGGGTCTAGTCTGAGTGCGTGTGGGGACCTCAGAACA
CTGTGACCTTAGCCCAGCAAGCCAGGCCCTTCATGAAGGCCAAGAAGGCTGCCACCATTC
CCTGCCAGCCCAAGAACTCCAGCTTCCCCACTGCCTCTGTGTGCCCCTTTGCGTCCTGTG
AAGGCCATTGAGAAATGCCCAGTGTGCCCCCTGGGAAAGGGCACGGCCTGTGCTCCTGAC
ACGGGCTGTGCTTGGCCACAGAACCACCCAGCGTCTCCCCTGCTGCTGTCCACGTCAGTT
CATGAGGCAACGTCGCGTGGTCTCAGACGTGGAGCAGCCAGCGGCAGCTCAGAGCAGGGC
ACTGTGTCCGGCGGAGCCAAGTCCACTCTGGGGGAGCTCTGGCGGGGACCACGGGCCACT
GCTCACCCACTGGCCCCGAGGGGGGTGTAGACGCCAAGACTCACGCATGTGTGACATCCG
GAGTCCTGGAGCCGGGTGTCCCAGTGGCACCACTAGGTGCCTGCTGCCTCCACAGTGGGG
TTCACACCCAGGGCTCCTTGGTCCCCCACAACCTGCCCCGGCCAGGCCTGCAGACCCAGA
CTCCAGCCAGACCTGCCTCACCCACCAATGCAGCCGGGGCTGGCGACACCAGCCAGGTGC
TGGTCTTGGGCCAGTTCTCCCACGACGGCTCACCCTCCCCTCCATCTGCGTTGATGCTCA
GAATCGCCTACCTGTGCCTGCGTGTAAACCACAGCCTCAGACCAGCTATGGGGAGAGGAC
AACACGGAGGATATCCAGCTTCCCCGGTCTGGGGTGAGGAATGTGGGGAGCTTGGGCATC
CTCCTCCAGCCTCCTCCAGCCCCCAGGCAGTGCCTTACCTGTGGTGCCCAGAAAAGTGCC
CCTAGGTTGGTGGGTCTACAGGAGCCTCAGCCAGGCAGCCCACCCCACCCTGGGGCCCTG
CCTCACCAAGGAAATAAAGACTCAAGCCATAAAAAAAA

FIGURE 182

MRPGAPGPLWPLPWGALAWAVGFVSSMGSGNPAPGGVCWLQQGQEATCSLVLQTDVTRAE
CCASGNIDTAWSNLTHPGNKINLLGFLGLVHCLPCKDSCDGVECGPGKACRMLGGRPRCE
CAPDCSGLPARLQVCGSDGATYRDECELRAARCRGHPDLSVMYRGRCRKSCEHVVCPRPQ
SCVVDQTGSAHCVVCRAAPCPVPSSPGQELCGNNNVTYISSCHMRQATCFLGRSIGVRHA
GSCAGTPEEPPGGESAEEEENFV

Important features:
Signal peptide:
amino acids 1-20

N-glycosylation sites:
amino acids 73-77, 215-219

Osteonectin domain proteins:
amino acids 97-130, 169-202

FIGURE 183

CACTCATTCATTCCAAAGGGTCTCTCAAGGCAATGGTAATGTGCAAGGAGGTGATACCTA
AATGAATGACCAAAAGAACATGCTTCTGCTTTTGTGTGTCTCCTACATTTTAGACATTTG
TTTGTTTCTCTTGGTAGCCTTTAAATTCCTTGAAGCCCAGGACCATGTCTCACTTACCTT
TGTGTTTCCACTAACTAGTCTACCTCCTGGAATTGGCAGATACTCAGTGAAAGCCTGTGA
AATAAGTGATGTCTATTTCTAGCATATTATTCTGAGATTTAATGATAGATTTAGTGATTG
AATGAGATTTCCATTTTCAAATACAGCAAAAGCATAACTATTTTCATTCATTCATATTCA
TTCAACTTCATTCTCAAAATTAGGTCCTGAGTTAACTAATAATTACCTTTGAAATGTGTG
GGTTATTTGAGGCAATCAGGTGGTGACATTGAGCTCTCAGCCAGAGTTTGTTTCTGGAAT
TGATTCAGTTCCATTGCATTGATTTTTGTTCTCAGAAGCCAAGGTTTCCCATGAAAAATC
ATTCCCACTTGAATTGGGCTGTGATTCTTGCTGCGTTTAAGTAAAGGAAGCCTCTTGGTT
CTAGTTCTGCAAACTTACACACTGAACTGGGACAAGTTTTTGTTTAGAGTAATGGCTGGG
AAAAGAGGAACCTTTCATTTTATTCAGAAGTCAAAAACAAAGGCCTCCCAGCCACCTGGA
GATGTTTTGTTGCAGACACCAGCCTGGCTCTGTCTTTATGCCTAACAATTGAGCATCCAG
TCTTCTTTGTGCTGGGACCATTGCTCAGCTCTGCAAGGGGAAAAGAGGGAGAAAGCCAGA
GCTGCCAGGCTTCTTGCACTGGGGCCGGGGGAGGGTTCCTGGGAAGCAGGTGCTCTCTGG
CTTCTTGGTACGTGAGGCTCTCGGAGCTGCCTCTCCTCTGACCCTCAGGTCCTCACCGAG
TTTGCTCCAGGAGTATATTGAAAACATACCCAGTGCTCTCTCAAGCACCCACTGCTTAGA
GGGCCCAGATTTCTTTTCCTTCTTTCCCTTGCAGAGCTGGAGACTGCATCGGGCATCTGG
TGTTTAAACTAAACAGGAAAACTGACTAAAGGTCCACAGTGCTCATTGTGTAGACTAGCT
GCCCTCCG**ATG**GGTGCTCTGATTATCAGTGGTTCCAGTGCAGGGCCTGTCACTAAACAGG
CCTCACTTCCTCCTTGGGGGCTTTCCCATGGGAGGTGTGGCTTTTTACTCTACATGGAAA
TGACTCTCTGCAGCCACAGAACACAGTCATTTTCTGAATTATCCCAGTCTCTCATGCGCC
CTGGATTCCTCCAGATGCCTTATATCTCTTGTGCAAAGTTGTCTAAAATTTGGTTCCCAG
CTTCCAAGCCTTGCCTTTTGGCCTTCCTGGAAGTATTTTTGTTGATGAGTCGTCTGTCAT
TATTCTCTAAAATGATTTGCTTTTTGTTTCTTTCATTCCTATTTCCACCCCACATATACA
CACATGCTTCT**TAA**CTTAGGGGATTACATGCCAATAAATCTATTGTTGAAAATGCACTAA
TACTATCGCAAAGACGAAAATTCACAGGCTGAACCGTTGTAAGTCCATATGCTCCTCAAC
TTACATGTGTGATGGAGTTATGCCCAAATAAGTCCATCGTCAAGTTGAAAAATCAAAATC
AAGCCATCTTAGGTTGAGGACCATTTGTTTGTACCTCCAAAGATGTCATATCTTTAAACA
TACTCCCTAGCTTTTCTTTTTACTTTTATTTTGAAGTAATTATAGAATCACAGAAAGTT
GCAAAAAA

FIGURE 184

MGALIISGSSAGPVTKQASLPPWGLSHGRCGFLLYMEMTLCSHRTQSFSELSQSLMRPGF
LQMPYISCAKLSKIWFPASKPCLLAFLEVFLLMSRLSLFSKMICFLFLSFLFPPHIYTHAS

Important features of the protein:
Signal peptide:
amino acids 1-41

Transmembrane domain:
amino acids 88-107

Casein kinase II phosphorylation site:
amino acids 47-50

N-myristoylation site:
amino acids 24-29

FIGURE 185

AACTCAAACTCCTCTCTCTGGGAAAACGCGGTGCTTGCTCCTCCCGGAGTGGCCTTGGCA
GGGTGTTGGAGCCCTCGGTCTGCCCCGTCCGGTCTCTGGGGCCAAGGCTGGGTTTCCCTC
ATGTATGGCAAGAGCTCTACTCGTGCGGTGCTTCTTCTCCTTGGCATACAGCTCACAGCT
CTTTGGCCTATAGCAGCTGTGGAAATTTATACCTCCCGGGTGCTGGAGGCTGTTAATGGG
ACAGATGCTCGGTTAAAATGCACTTTCTCCAGCTTTGCCCCTGTGGGTGATGCTCTAACA
GTGACCTGGAATTTTCGTCCTCTAGACGGGGGACCTGAGCAGTTTGTATTCTACTACCAC
ATAGATCCCTTCCAACCCATGAGTGGGCGGTTTAAGGACCGGGTGTCTTGGGATGGGAAT
CCTGAGCGGTACGATGCCTCCATCCTTCTCTGGAAACTGCAGTTCGACGACAATGGGACA
TACACCTGCCAGGTGAAGAACCCACCTGATGTTGATGGGGTGATAGGGGAGATCCGGCTC
AGCGTCGTGCACACTGTACGCTTCTCTGAGATCCACTTCCTGGCTCTGGCCATTGGCTCT
GCCTGTGCACTGATGATCATAATAGTAATTGTAGTGGTCCTCTTCCAGCATTACCGGAAA
AAGCGATGGGCCGAAAGAGCTCATAAAGTGGTGGAGATAAAATCAAAAGAAGAGGAAAGG
CTCAACCAAGAGAAAAAGGTCTCTGTTTATTTAGAAGACACAGAC**TAA**CAATTTTAGATG
GAAGCTGAGATGATTTCCAAGAACAAGAACCCTAGTATTTCTTGAAGTTAATGGAAACTT
TTCTTTGGCTTTTCCAGTTGTGACCCGTTTTCCAACCAGTTCTGCAGCATATTAGATTCT
AGACAAGCAACACCCCTCTGGAGCCAGCACAGTGCTCCTCCATATCACCAGTCATACACA
GCCTCATTATTAAGGTCTTATTTAATTTCAGAGTGTAAATTTTTTCAAGTGCTCATTAGG
TTTTATAAACAAGAAGCTACATTTTTGCCCTTAAGACACTACTTACAGTGTTATGACTTG
TATACACATATATTGGTATCAAAGGGGATAAAAGCCAATTTGTCTGTTACATTTCCTTTC
ACGTATTTCTTTTAGCAGCACTTCTGCTACTAAAGTTAATGTGTTTACTCTCTTTCCTTC
CCACATTCTCAATTAAAAGGTGAGCTAAGCCTCCTCGGTGTTTCTGATTAACAGTAAATC
CTAAATTCAAACTGTTAAATGACATTTTTATTTTTATGTCTCTCCTTAACTATGAGACAC
ATCTTGTTTTACTGAATTTCTTTCAATATTCCAGGTGATAGATTTTTGTCG

FIGURE 186

MYGKSSTRAVLLLLGIQLTALWPIAAVEIYTSRVLEAVNGTDARLKCTFSSFAPVGDALT
VTWNFRPLDGGPEQFVFYYHIDPFQPMSGRFKDRVSWDGNPERYDASILLWKLQFDDNGT
YTCQVKNPPDVDGVIGEIRLSVVHTVRFSEIHFLALAIGSACALMIIIVIVVVLFQHYRK
KRWAERAHKVVEIKSKEEERLNQEKKVSVYLEDTD

FIGURE 187

GCATTTTTGTCTGTGCTCCCTGATCTTCAGGTCACCACC**ATG**AAGTTCTTAGCAGTCCTG
GTACTCTTGGGAGTTTCCATCTTTCTGGTCTCTGCCCAGAATCCGACAACAGCTGCTCCA
GCTGACACGTATCCAGCTACTGGTCCTGCTGATGATGAAGCCCCTGATGCTGAAACCACT
GCTGCTGCAACCACTGCGACCACTGCTGCTCCTACCACTGCAACCACCGCTGCTTCTACC
ACTGCTCGTAAAGACATTCCAGTTTTACCCAAATGGGTTGGGGATCTCCCGAATGGTAGA
GTGTGTCCC**TGA**GATGGAATCAGCTTGAGTCTTCTGCAATTGGTCACAACTATTCATGCT
TCCTGTGATTTCATCCAACTACTTACCTTGCCTACGATATCCCCTTTATCTCTAATCAGT
TTATTTTCTTTCAAATAAAAAATAACTATGAGCAACATAAAAAAAAAAAAA

FIGURE 188

MKFLAVLVLLGVSIFLVSAQNPTTAAPADTYPATGPADDEAPDAETTAAATTATTAAPTT
ATTAASTTARKDIPVLPKWVGDLPNGRVCP

FIGURE 189

GAGCGAAC<u>ATG</u>GCAGCGCGTTGGCGGTTTTGGTGTGTCTCTGTGACCATGGTGGTGGCGC
TGCTCATCGTTTGCGACGTTCCCTCAGCCTCTGCCCAAAGAAAGAAGGAGATGGTGTTAT
CTGAAAAGGTTAGTCAGCTGATGGAATGGACTAACAAAAGACCTGTAATAAGAATGAATG
GAGACAAGTTCCGTCGCCTTGTGAAAGCCCCACCGAGAAATTACTCCGTTATCGTCATGT
TCACTGCTCTCCAACTGCATAGACAGTGTGTCGTTTGCAAGCAAGCTGATGAAGAATTCC
AGATCCTGGCAAACTCCTGGCGATACTCCAGTGCATTCACCAACAGGATATTTTTTGCCA
TGGTGGATTTTGATGAAGGCTCTGATGTATTTCAGATGCTAAACATGAATTCAGCTCCAA
CTTTCATCAACTTTCCTGCAAAAGGGAAACCCAAACGGGGTGATACATATGAGTTACAGG
TGCGGGGTTTTTCAGCTGAGCAGATTGCCCGGTGGATCGCCGACAGAACTGATGTCAATA
TTAGAGTGATTAGACCCCCAAATTATGCTGGTCCCCTTATGTTGGGATTGCTTTTGGCTG
TTATTGGTGGACTTGTGTATCTTCGAAGAAGTAATATGGAATTTCTCTTTAATAAAACTG
GATGGGCTTTTGCAGCTTTGTGTTTTGTGCTTGCTATGACATCTGGTCAAATGTGGAACC
ATATAAGAGGACCACCATATGCCCATAAGAATCCCCACACGGGACATGTGAATTATATCC
ATGGAAGCAGTCAAGCCCAGTTTGTAGCTGAAACACACATTGTTCTTCTGTTTAATGGTG
GAGTTACCTTAGGAATGGTGCTTTTATGTGAAGCTGCTACCTCTGACATGGATATTGGAA
AGCGAAAGATAATGTGTGTGGCTGGTATTGGACTTGTTGTATTATTCTTCAGTTGGATGC
TCTCTATTTTTAGATCTAAATATCATGGCTACCCATACAGCTTTCTGATGAGT<u>TAA</u>AAAG
GTCCCAGAGATATATAGACACTGGAGTACTGGAAATTGAAAAACGAAAATCGTGTGTGTT
TGAAAAGAAGAATGCAACTTGTATATTTTGTATTACCTCTTTTTTTCAAGTGATTTAAAT
AGTTAATCATTTAACCAAAGAAGATGTGTAGTGCCTTAACAAGCAATCCTCTGTCAAAAT
CTGAGGTATTTGAAAATAATTATCCTCTTAACCTTCTCTTCCCAGTGAACTTTATGGAAC
ATTTAATTTAGTACAATTAAGTATATTATAAAAATTGTAAAACTACTACTTTGTTTTAGT
TAGAACAAAGCTCAAAACTACTTTAGTTAACTTGGTCATCTGATTTTATATTGCCTTATC
CAAAGATGGGGAAAGTAAGTCCTGACCAGGTGTTCCCACATATGCCTGTTACAGATAACT
ACATTAGGAATTCATTCTTAGCTTCTTCATCTTTGTGTGGATGTGTATACTTTACGCATC
TTTCCTTTTGAGTAGAGAAATTATGTGTGTCATGTGGTCTTCTGAAAATGGAACACCATT
CTTCAGAGCACACGTCTAGCCCTCAGCAAGACAGTTGTTTCTCCTCCTCCTTGCATATTT
CCTACTGCGCTCCAGCCTGAGTGATAGAGTGAGACTCTGTCTCAAAAAAAAAGTATCTCTA
AATACAGGATTATAATTTCTGCTTGAGTATGGTGTTAACTACCTTGTATTTAGAAAGATT
TCAGATTCATTCCATCTCCTTAGTTTTCTTTTAAGGTGACCCATCTGTGATAAAAATATA
GCTTAGTGCTAAAATCAGTGTAACTTATACATGGCCTAAAATGTTTCTACAAATTAGAGT
TTGTCACTTATTCCATTTGTACCTAAGAGAAAAATAGGCTCAGTTAGAAAAGGACTCCCT
GGCCAGGCGCAGTGACTTACGCCTGTAATCTCAGCACTTTGGGAGGCCAAGGCAGGCAGA
TCACGAGGTCAGGAGTTCGAGACCATCCTGGCCAACATGGTGAAACCCCGTCTCTACTAA
AAATATAAAAATTAGCTGGGTGTGGTGGCAGGAGCCTGTAATCCCAGCTACACAGGAGGC
TGAGGCACGAGAATCACTTGAACTCAGGAGATGGAGGTTTCAGTGAGCCGAGATCACGCC
ACTGCACTCCAGCCTGGCAACAGAGCGAGACTCCATCTCAAAAAAAAAAAAAA

FIGURE 190

MAARWRFWCVSVTMVVALLIVCDVPSASAQRKKEMVLSEKVSQLMEWTNKRPVIRMNGDK
FRRLVKAPPRNYSVIVMFTALQLHRQCVVCKQADEEFQILANSWRYSSAFTNRIFFAMVD
FDEGSDVFQMLNMNSAPTFINFPAKGKPKRGDTYELQVRGFSAEQIARWIADRTDVNIRV
IRPPNYAGPLMLGLLLAVIGGLVYLRRSNMEFLFNKTGWAFAALCFVLAMTSGQMWNHIR
GPPYAHKNPHTGHVNYIHGSSQAQFVAETHIVLLFNGGVTLGMVLLCEAATSDMDIGKRK
IMCVAGIGLVVLFFSWMLSIFRSKYHGYPYSFLMS

Signal peptide:
amino acids 1-29

Transmembrane domains:
amino acids 183-205, 217-237, 217-287, 301-321

FIGURE 191

GAGAGAAGTCAGCCTGGCAGAGAGACTCTGAAATGAGGGATTAGAGGTGTTCAAGGAGCA
AGAGCTTCAGCCTGAAGACAAGGGAGCAGTCCCTGAAGACGCTTCTACTGAGAGGTCTGC
CATGGCCTCTCTTGGCCTCCAACTTGTGGGCTACATCCTAGGCCTTCTGGGGCTTTTGGG
CACACTGGTTGCCATGCTGCTCCCCAGCTGGAAAACAAGTTCTTATGTCGGTGCCAGCAT
TGTGACAGCAGTTGGCTTCTCCAAGGGCCTCTGGATGGAATGTGCCACACACAGCACAGG
CATCACCCAGTGTGACATCTATAGCACCCTTCTGGGCCTGCCCGCTGACATCCAGGCTGC
CCAGGCCATGATGGTGACATCCAGTGCAATCTCCTCCCTGGCCTGCATTATCTCTGTGGT
GGGCATGAGATGCACAGTCTTCTGCCAGGAATCCCGAGCCAAAGACAGAGTGGCGGTAGC
AGGTGGAGTCTTTTTCATCCTTGGAGGCCTCCTGGGATTCATTCCTGTTGCCTGGAATCT
TCATGGGATCCTACGGGACTTCTACTCACCACTGGTGCCTGACAGCATGAAATTTGAGAT
TGGAGAGGCTCTTTACTTGGGCATTATTTCTTCCCTGTTCTCCCTGATAGCTGGAATCAT
CCTCTGCTTTTCCTGCTCATCCCAGAGAAATCGCTCCAACTACTACGATGCCTACCAAGC
CCAACCTCTTGCCACAAGGAGCTCTCCAAGGCCTGGTCAACCTCCCAAAGTCAAGAGTGA
GTTCAATTCCTACAGCCTGACAGGGTATGTGTGAAGAACCAGGGGCCAGAGCTGGGGGGT
GGCTGGGTCTGTGAAAAACAGTGGACAGCACCCCGAGGGCCACAGGTGAGGGACACTACC
ACTGGATCGTGTCAGAAGGTGCTGCTGAGGATAGACTGACTTTGGCCATTGGATTGAGCA
AAGGCAGAAATGGGGGCTAGTGTAACAGCATGCAGGTTGAATTGCCAAGGATGCTCGCCA
TGCCAGCCTTTCTGTTTTCCTCACCTTGCTGCTCCCCTGCCCTAAGTCCCCAACCCTCAA
CTTGAAACCCCATTCCCTTAAGCCAGGACTCAGAGGATCCCTTTGCCCTCTGGTTTACCT
GGGACTCCATCCCCAAACCCACTAATCACATCCCACTGACTGACCCTCTGTGATCAAAGA
CCCTCTCTCTGGCTGAGGTTGGCTCTTAGCTCATTGCTGGGGATGGGAAGGAGAAGCAGT
GGCTTTTGTGGGCATTGCTCTAACCTACTTCTCAAGCTTCCCTCCAAAGAAACTGATTGG
CCCTGGAACCTCCATCCCACTCTTGTTATGACTCCACAGTGTCCAGACTAATTTGTGCAT
GAACTGAAATAAAACCATCCTACGGTATCCAGGGAACAGAAAGCAGGATGCAGGATGGGA
GGACAGGAAGGCAGCCTGGGACATTTAAAAAAATA

FIGURE 192

MASLGLQLVGYILGLLGLLGTLVAMLLPSWKTSSYVGASIVTAVGFSKGLWMECATHSTG
ITQCDIYSTLLGLPADIQAAQAMMVTSSAISSLACIISVVGMRCTVFCQESRAKDRVAVA
GGVFFILGGLLGFIPVAWNLHGILRDFYSPLVPDSMKFEIGEALYLGIISSLFSLIAGII
LCFSCSSQRNRSNYYDAYQAQPLATRSSPRPGQPPKVKSEFNSYSLTGYV

Important features of the protein:
Signal peptide:
amino acids 1-24

Transmembrane domains:
amino acids 82-102, 117-140, 163-182

N-glycosylation site:
amino acids 190-193

PMP-22 / EMP / MP20 family proteins:
amino acids 46-59

FIGURE 193

CTCCACTGCAACCACCCAGAGCC**ATG**GCTCCCCGAGGCTGCATCGTAGCTGTCTTTGCCA
TTTTCTGCATCTCCAGGCTCCTCTGCTCACACGGAGCCCCAGTGGCCCCCATGACTCCTT
ACCTGATGCTGTGCCAGCCACACAAGAGATGTGGGGACAAGTTCTACGACCCCCTGCAGC
ACTGTTGCTATGATGATGCCGTCGTGCCCTTGGCCAGGACCCAGACGTGTGGAAACTGCA
CCTTCAGAGTCTGCTTTGAGCAGTGCTGCCCCTGGACCTTCATGGTGAAGCTGATAAACC
AGAACTGCGACTCAGCCCGGACCTCGGATGACAGGCTTTGTCGCAGTGTCAGC**TAA**TGGA
ACATCAGGGGAACGATGACTCCTGGATTCTCCTTCCTGGGTGGGCCTGGAGAAAGAGGCT
GGTGTTACCTGAGATCTGGGATGCTGAGTGGCTGTTTGGGGGCCAGAGAAACACACACTC
AACTGCCCACTTCATTCTGTGACCTGTCTGAGGCCCACCCTGCAGCTGCCCTGAGGAGGC
CCACAGGTCCCCTTCTAGAATTCTGGACAGCATGAGATGCGTGTGCTGATGGGGGCCCAG
GGACTCTGAACCCTCCTGATGACCCCTATGGCCAACATCAACCCGGCACCACCCCAAGGC
TGGCTGGGGAACCCTTCACCCTTCTGTGAGATTTTCCATCATCTCAAGTTCTCTTCTATC
CAGGAGCAAAGCACAGGATCATAATAAATTTATGTACTTTATAAATGAAAA

FIGURE 194

MAPRGCIVAVFAIFCISRLLCSHGAPVAPMTPYLMLCQPHKRCGDKFYDPLQHCCYDDAV
VPLARTQTCGNCTFRVCFEQCCPWTFMVKLINQNCDSARTSDDRLCRSVS

Signal peptide:
amino acids 1-24

FIGURE 195

CATTTCCAACAAGAGCACTGGCCAAGTCAGCTTCTTCTGAGAGAGTCTCTAGAAGAC**ATG**
ATGCTACACTCAGCTTTGGGTCTCTGCCTCTTACTCGTCACAGTTTCTTCCAACCTTGCC
ATTGCAATAAAAAAGGAAAAGAGGCCTCCTCAGACACTCTCAAGAGGATGGGGAGATGAC
ATCACTTGGGTACAAACTTATGAAGAAGGTCTCTTTTATGCTCAAAAAAGTAAGAAGCCA
TTAATGGTTATTCATCACCTGGAGGATTGTCAATACTCTCAAGCACTAAAGAAAGTATTT
GCCCAAAATGAAGAAATACAAGAAATGGCTCAGAATAAGTTCATCATGCTAAACCTTATG
CATGAAACCACTGATAAGAATTTATCACCTGATGGGCAATATGTGCCTAGAATCATGTTT
GTAGACCCTTCTTTAACAGTTAGAGCTGACATAGCTGGAAGATACTCTAACAGATTGTAC
ACATATGAGCCTCGGGATTTACCCCTATTGATAGAAAACATGAAGAAAGCATTAAGACTT
ATTCAGTCAGAGCTA**TAA**GAGATGATGGAAAAAAGCCTTCACTTCAAAGAAGTCAAATTT
CATGAAGAAAACCTCTGGCACATTGACAAATACTAAATGTGCAAGTATATAGATTTTGTA
ATATTACTATTTAGTTTTTTTAATGTGTTTGCAATAGTCTTATTAAAATAAATGTTTTTT
AAATCTGA

FIGURE 196

MMLHSALGLCLLLVTVSSNLAIAIKKEKRPPQTLSRGWGDDITWVQTYEEGLFYAQKSKK
PLMVIHHLEDCQYSQALKKVFAQNEEIQEMAQNKFIMLNLMHETTDKNLSPDGQYVPRIM
FVDPSLTVRADIAGRYSNRLYTYEPRDLPLLIENMKKALRLIQSEL

Important features:
Signal peptide:
amino acids 1-23

N-myristoylation site:
amino acids 51-57

FIGURE 197

GGGGGCGGGTGCCTGGAGCACGGCGCTGGGGCCGCCCGCAGCGCTCACTCGCTCGCACTC
AGTCGCGGGAGGCTTCCCCGCGCCGGCCGCGTCCCGCCCGCTCCCCGGCACCAGAAGTTC
CTCTGCGCGTCCGACGGCGAC**ATG**GGCGTCCCCACGGCCCTGGAGGCCGGCAGCTGGCGC
TGGGGATCCCTGCTCTTCGCTCTCTTCCTGGCTGCGTCCCTAGGTCCGGTGGCAGCCTTC
AAGGTCGCCACGCCGTATTCCCTGTATGTCTGTCCCGAGGGGCAGAACGTCACCCTCACC
TGCAGGCTCTTGGGCCCTGTGGACAAAGGGCACGATGTGACCTTCTACAAGACGTGGTAC
CGCAGCTCGAGGGGCGAGGTGCAGACCTGCTCAGAGCGCCGGCCCATCCGCAACCTCACG
TTCCAGGACCTTCACCTGCACCATGGAGGCCACCAGGCTGCCAACACCAGCCACGACCTG
GCTCAGCGCCACGGGCTGGAGTCGGCCTCCGACCACCATGGCAACTTCTCCATCACCATG
CGCAACCTGACCCTGCTGGATAGCGGCCTCTACTGCTGCCTGGTGGTGGAGATCAGGCAC
CACCACTCGGAGCACAGGGTCCATGGTGCCATGGAGCTGCAGGTGCAGACAGGCAAAGAT
GCACCATCCAACTGTGTGGTGTACCCATCCTCCTCCCAGGATAGTGAAAACATCACGGCT
GCAGCCCTGGCTACGGGTGCCTGCATCGTAGGAATCCTCTGCCTCCCCCTCATCCTGCTC
CTGGTCTACAAGCAAAGGCAGGCAGCCTCCAACCGCCGTGCCCAGGAGCTGGTGCGGATG
GACAGCAACATTCAAGGGATTGAAAACCCCGGCTTTGAAGCCTCACCACCTGCCCAGGGG
ATACCCGAGGCCAAAGTCAGGCACCCCCTGTCCTATGTGGCCCAGCGGCAGCCTTCTGAG
TCTGGGCGGCATCTGCTTTCGGAGCCCAGCACCCCCCTGTCTCCTCCAGGCCCCGGAGAC
GTCTTCTTCCCATCCCTGGACCCTGTCCCTGACTCTCCAAACTTTGAGGTCATC**TAG**CCC
AGCTGGGGGACAGTGGGCTGTTGTGGCTGGGTCTGGGGCAGGTGCATTTGAGCCAGGGCT
GGCTCTGTGAGTGGCCTCCTTGGCCTCGGCCCTGGTTCCCTCCCTCCTGCTCTGGGCTCA
GATACTGTGACATCCCAGAAGCCCAGCCCCTCAACCCCTCTGGATGCTACATGGGGATGC
TGGACGGCTCAGCCCCTGTTCCAAGGATTTTGGGGTGCTGAGATTCTCCCCTAGAGACCT
GAAATTCACCAGCTACAGATGCCAAATGACTTACATCTTAAGAAGTCTCAGAACGTCCAG
CCCTTCAGCAGCTCTCGTTCTGAGACATGAGCCTTGGGATGTGGCAGCATCAGTGGGACA
AGATGGACACTGGGCCACCCTCCCAGGCACCAGACACAGGGCACGGTGGAGAGACTTCTC
CCCCGTGGCCGCCTTGGCTCCCCCGTTTTGCCCGAGGCTGCTCTTCTGTCAGACTTCCTC
TTTGTACCACAGTGGCTCTGGGGCCAGGCCTGCCTGCCCACTGGCCATCGCCACCTTCCC
CAGCTGCCTCCTACCAGCAGTTTCTCTGAAGATCTGTCAACAGGTTAAGTCAATCTGGGG
CTTCCACTGCCTGCATTCCAGTCCCCAGAGCTTGGTGGTCCCGAAACGGGAAGTACATAT
TGGGGCATGGTGGCCTCCGTGAGCAAATGGTGTCTTGGGCAATCTGAGGCCAGGACAGAT
GTTGCCCCACCCACTGGAGATGGTGCTGAGGGAGGTGGGTGGGGCCTTCTGGGAAGGTGA
GTGGAGAGGGGCACCTGCCCCCCGCCCTCCCCATCCCCTACTCCCACTGCTCAGCGCGGG
CCATTGCAAGGGTGCCACACAATGTCTTGTCCACCCTGGGACACTTCTGAGTATGAAGCG
GGATGCTATTAAAAACTACATGGGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAGA

FIGURE 198

MGVPTALEAGSWRWGSLLFALFLAASLGPVAAFKVATPYSLYVCPEGQNVTLTCRLLGPV
DKGHDVTFYKTWYRSSRGEVQTCSERRPIRNLTFQDLHLHHGGHQAANTSHDLAQRHGLE
SASDHHGNFSITMRNLTLLDSGLYCCLVVEIRHHHSEHRVHGAMELQVQTGKDAPSNCVV
YPSSSQDSENITAAALATGACIVGILCLPLILLLVYKQRQAASNRRAQELVRMDSNIQGI
ENPGFEASPPAQGIPEAKVRHPLSYVAQRQPSESGRHLLSEPSTPLSPPGPGDVFFPSLD
PVPDSPNFEVI

Signal peptide:
amino acids 1-28

Transmembrane domain:
amino acids 190-216

FIGURE 199

CTAGCCTGCGCCAAGGGGTAGTGAGACCGCGCGGCAACAGCTTGCGGCTGCGGGGAGCTC
CCGTGGGCGCTCCGCTGGCTGTGCAGGCGGCC**ATG**GATTCCTTGCGGAAAATGCTGATCT
CAGTCGCAATGCTGGGCGCAGGGGCTGGCGTGGGCTACGCGCTCCTCGTTATCGTGACCC
CGGGAGAGCGGCGGAAGCAGGAAATGCTAAAGGAGATGCCACTGCAGGACCCAAGGAGCA
GGGAGGAGGCGGCCAGGACCCAGCAGCTATTGCTGGCCACTCTGCAGGAGGCAGCGACCA
CGCAGGAGAACGTGGCCTGGAGGAAGAACTGGATGGTTGGCGGCGAAGGCGGCGCCAGCG
GGAGGTCACCG**TGA**GACCGGACTTGCCTCCGTGGGCGCCGGACCTTGGCTTGGGCGCAGG
AATCCGAGGCAGCCTTTCTCCTTCGTGGGCCCAGCGGAGAGTCCGGACCGAGATACCATG
CCAGGACTCTCCGGGGTCCTGTGAGCTGCCGTCGGGTGAGCACGTTTCCCCCAAACCCTG
GACTGACTGCTTTAAGGTCCGCAAGGCGGGCCAGGGCCGAGACGCGAGTCGGATGTGGTG
AACTGAAAGAACCAATAAAATCATGTTCCTCCAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 200

MDSLRKMLISVAMLGAGAGVGYALLVIVTPGERRKQEMLKEMPLQDPRSREEAARTQQLL
LATLQEAATTQENVAWRKNWMVGGEGGASGRSP

Signal peptide:
amino acids 1-18

FIGURE 201

GACAGCTGTGTCTCGATGGAGTAGACTCTCAGAACAGCGCAGTTTGCCCTCCGCTCACGC
AGAGCCTCTCCGTGGCTTCCGCACCTTGAGCATTAGGCCAGTTCTCCTCTTCTCTCTAAT
CCATCCGTCACCTCTCCTGTCATCCGTTTCCATGCCGTGAGGTCCATTCACAGAACACAT
CC**ATG**GCTCTCATGCTCAGTTTGGTTCTGAGTCTCCTCAAGCTGGGATCAGGGCAGTGGC
AGGTGTTTGGGCCAGACAAGCCTGTCCAGGCCTTGGTGGGGGAGGACGCAGCATTCTCCT
GTTTCCTGTCTCCTAAGACCAATGCAGAGGCCATGGAAGTGCGGTTCTTCAGGGGCCAGT
TCTCTAGCGTGGTCCACCTCTACAGGGACGGGAAGGACCAGCCATTTATGCAGATGCCAC
AGTATCAAGGCAGGACAAAACTGGTGAAGGATTCTATTGCGGAGGGGCGCATCTCTCTGA
GGCTGGAAAACATTACTGTGTTGGATGCTGGCCTCTATGGGTGCAGGATTAGTTCCCAGT
CTTACTACCAGAAGGCCATCTGGGAGCTACAGGTGTCAGCACTGGGCTCAGTTCCTCTCA
TTTCCATCACGGGATATGTTGATAGAGACATCCAGCTACTCTGTCAGTCCTCGGGCTGGT
TCCCCCGGCCCACAGCGAAGTGGAAAGGTCCACAAGGACAGGATTTGTCCACAGACTCCA
GGACAAACAGAGACATGCATGGCCTGTTTGATGTGGAGATCTCTCTGACCGTCCAAGAGA
ACGCCGGGAGCATATCCTGTTCCATGCGGCATGCTCATCTGAGCCGAGAGGTGGAATCCA
GGGTACAGATAGGAGATACCTTTTTCGAGCCTATATCGTGGCACCTGGCTACCAAAGTAC
TGGGAATACTCTGCTGTGGCCTATTTTTTGGCATTGTTGGACTGAAGATTTTCTTCTCCA
AATTCCAGTGGAAAATCCAGGCGGAACTGGACTGGAGAAGAAAGCACGGACAGGCAGAAT
TGAGAGACGCCCGGAAACACGCAGTGGAGGTGACTCTGGATCCAGAGACGGCTCACCCGA
AGCTCTGCGTTTCTGATCTGAAAACTGTAACCCATAGAAAAGCTCCCCAGGAGGTGCCTC
ACTCTGAGAAGAGATTTACAAGGAAGAGTGTGGTGGCTTCTCAGAGTTTCCAAGCAGGGA
AACATTACTGGGAGGTGGACGGAGGACACAATAAAAGGTGGCGCGTGGGAGTGTGCCGGG
ATGATGTGGACAGGAGGAAGGAGTACGTGACTTTGTCTCCCGATCATGGGTACTGGGTCC
TCAGACTGAATGGAGAACATTTGTATTTCACATTAAATCCCCGTTTTATCAGCGTCTTCC
CCAGGACCCCACCTACAAAAATAGGGGTCTTCCTGGACTATGAGTGTGGGACCATCTCCT
TCTTCAACATAAATGACCAGTCCCTTATTTATACCCTGACATGTCGGTTTGAAGGCTTAT
TGAGGCCCTACATTGAGTATCCGTCCTATAATGAGCAAAATGGAACTCCCATAGTCATCT
GCCCAGTCACCCAGGAATCAGAGAAAGAGGCCTCTTGGCAAAGGGCCTCTGCAATCCCAG
AGACAAGCAACAGTGAGTCCTCCTCACAGGCAACCACGCCCTTCCTCCCCAGGGGTGAAA
TG**TAG**GATGAATCACATCCCACATTCTTCTTTAGGGATATTAAGGTCTCTCTCCCAGATC
CAAAGTCCCGCAGCAGCCGGCCAAGGTGGCTTCCAGATGAAGGGGGACTGGCCTGTCCAC
ATGGGAGTCAGGTGTCATGGCTGCCCTGAGCTGGGAGGGAAGAAGGCTGACATTACATTT
AGTTTGCTCTCACTCCATCTGGCTAAGTGATCTTGAAATACCACCTCTCAGGTGAAGAAC
CGTCAGGAATTCCCATCTCACAGGCTGTGGTGTAGATTAAGTAGACAAGGAATGTGAATA
ATGCTTAGATCTTATTGATGACAGAGTGTATCCTAATGGTTTGTTCATTATATTACACTT
TCAGTAAAAAAA

FIGURE 202

MALMLSLVLSLLKLGSGQWQVFGPDKPVQALVGEDAAFSCFLSPKTNAEAMEVRFFRGQF
SSVVHLYRDGKDQPFMQMPQYQGRTKLVKDSIAEGRISLRLENITVLDAGLYGCRISSQS
YYQKAIWELQVSALGSVPLISITGYVDRDIQLLCQSSGWFPRPTAKWKGPQGQDLSTDSR
TNRDMHGLFDVEISLTVQENAGSISCSMRHAHLSREVESRVQIGDTFFEPISWHLATKVL
GILCCGLFFGIVGLKIFFSKFQWKIQAELDWRRKHGQAELRDARKHAVEVTLDPETAHPK
LCVSDLKTVTHRKAPQEVPHSEKRFTRKSVVASQSFQAGKHYWEVDGGHNKRWRVGVCRD
DVDRRKEYVTLSPDHGYWVLRLNGEHLYFTLNPRFISVFPRTPPTKIGVFLDYECGTISF
FNINDQSLIYTLTCRFEGLLRPYIEYPSYNEQNGTPIVICPVTQESEKEASWQRASAIPE
TSNSESSSQATTPFLPRGEM

Signal peptide:
amino acids 1-17

Transmembrane domain:
amino acids 239-255

FIGURE 203

TGCGGCGCAGTGTAGACCTGGGAGG<u>ATG</u>GGCGGCCTGCTGCTGGCTGCTTTTCTGGCTTT
GGTCTCGGTGCCCAGGGCCCAGGCCGTGTGGTTGGGAAGACTGGACCCTGAGCAGCTTCT
TGGGCCCTGGTACGTGCTTGCGGTGGCCTCCCGGGAAAAGGGCTTTGCCATGGAGAAGGA
CATGAAGAACGTCGTGGGGGTGGTGGTGACCCTCACTCCAGAAAACAACCTGCGGACGCT
GTCCTCTCAGCACGGGCTGGGAGGGTGTGACCAGAGTGTCATGGACCTGATAAAGCGAAA
CTCCGGATGGGTGTTTGAGAATCCCTCAATAGGCGTGCTGGAGCTCTGGGTGCTGGCCAC
CAACTTCAGAGACTATGCCATCATCTTCACTCAGCTGGAGTTCGGGGACGAGCCCTTCAA
CACCGTGGAGCTGTACAGTCTGACGGAGACAGCCAGCCAGGAGGCCATGGGGCTCTTCAC
CAAGTGGAGCAGGAGCCTGGGCTTCCTGTCACAG<u>TAG</u>CAGGCCCAGCTGCAGAAGGACCT
CACCTGTGCTCACAAGATCCTTCTGTGAGTGCTGCGTCCCCAGTAGGGATGGCGCCCACA
GGGTCCTGTGACCTCGGCCAGTGTCCACCCACCTCGCTCAGCGGCTCCCGGGGCCCAGCA
CCAGCTCAGAATAAAGCGATTCCACAGCA

FIGURE 204

MGGLLLAAFLALVSVPRAQAVWLGRLDPEQLLGPWYVLAVASREKGFAMEKDMKNVVGVV
VTLTPENNLRTLSSQHGLGGCDQSVMDLIKRNSGWVFENPSIGVLELWVLATNFRDYAII
FTQLEFGDEPFNTVELYSLTETASQEAMGLFTKWSRSLGFLSQ

Signal peptide:
amino acids 1-20

FIGURE 205

GACGCCCAGTGACCTGCCGAGGTCGGCAGCACAGAGCTCTGGAG**ATG**AAGACCCTGTTCC
TGGGTGTCACGCTCGGCCTGGCCGCTGCCCTGTCCTTCACCCTGGAGGAGGAGGATATCA
CAGGGACCTGGTACGTGAAGGCCATGGTGGTCGATAAGGACTTTCCGGAGGACAGGAGGC
CCAGGAAGGTGTCCCCAGTGAAGGTGACAGCCCTGGGCGGTGGGAAGTTGGAAGCCACGT
TCACCTTCATGAGGGAGGATCGGTGCATCCAGAAGAAAATCCTGATGCGGAAGACGGAGG
AGCCTGGCAAATACAGCGCCTATGGGGGCAGGAAGCTCATGTACCTGCAGGAGCTGCCCA
GGAGGGACCACTACATCTTTTACTGCAAAGACCAGCACCATGGGGGCCTGCTCCACATGG
GAAAGCTTGTGGGTAGGAATTCTGATACCAACCGGGAGGCCCTGGAAGAATTTAAGAAAT
TGGTGCAGCGCAAGGGACTCTCGGAGGAGGACATTTTCACGCCCCTGCAGACGGGAAGCT
GCGTTCCCGAACAC**TAG**GCAGCCCCCGGGTCTGCACCTCCAGAGCCCACCCTACCACCAG
ACACAGAGCCCGGACCACCTGGACCTACCCTCCAGCCATGACCCTTCCCTGCTCCCACCC
ACCTGACTCCAAATAAAGTCCTTTTCCCCCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAA

FIGURE 206

MKTLFLGVTLGLAAALSFTLEEEDITGTWYVKAMVVDKDFPEDRRPRKVSPVKVTALGGG
KLEATFTFMREDRCIQKKILMRKTEEPGKYSAYGGRKLMYLQELPRRDHYIFYCKDQHHG
GLLHMGKLVGRNSDTNREALEEFKKLVQRKGLSEEDIFTPLQTGSCVPEH

Important features:
Signal peptide:
amino acids 1-17

FIGURE 207

GTTCCGCAGATGCAGAGGTTGAGGTGGCTGCGGGACTGGAAGTCATCGGGCAGAGGTCTC
ACAGCAGCCAAGGAACCTGGGGCCCGCTCCTCCCCCCTCCAGGCC<u>ATG</u>AGGATTCTGCAG
TTAATCCTGCTTGCTCTGGCAACAGGGCTTGTAGGGGGAGAGACCAGGATCATCAAGGGG
TTCGAGTGCAAGCCTCACTCCCAGCCCTGGCAGGCAGCCCTGTTCGAGAAGACGCGGCTA
CTCTGTGGGGCGACGCTCATCGCCCCCAGATGGCTCCTGACAGCAGCCCACTGCCTCAAG
CCCCGCTACATAGTTCACCTGGGGCAGCACAACCTCCAGAAGGAGGAGGGCTGTGAGCAG
ACCCGGACAGCCACTGAGTCCTTCCCCCACCCCGGCTTCAACAACAGCCTCCCCAACAAA
GACCACCGCAATGACATCATGCTGGTGAAGATGGCATCGCCAGTCTCCATCACCTGGGCT
GTGCGACCCCTCACCCTCTCCTCACGCTGTGTCACTGCTGGCACCAGCTGCCTCATTTCC
GGCTGGGGCAGCACGTCCAGCCCCCAGTTACGCCTGCCTCACACCTTGCGATGCGCCAAC
ATCACCATCATTGAGCACCAGAAGTGTGAGAACGCCTACCCCGGCAACATCACAGACACC
ATGGTGTGTGCCAGCGTGCAGGAAGGGGGCAAGGACTCCTGCCAGGGTGACTCCGGGGGC
CCTCTGGTCTGTAACCAGTCTCTTCAAGGCATTATCTCCTGGGGCCAGGATCCGTGTGCG
ATCACCCGAAAGCCTGGTGTCTACACGAAAGTCTGCAAATATGTGGACTGGATCCAGGAG
ACGATGAAGAACAAT<u>TAG</u>ACTGGACCCACCCACCACAGCCCATCACCCTCCATTTCCACT
TGGTGTTTGGTTCCTGTTCACTCTGTTAATAAGAAACCCTAAGCCAAGACCCTCTACGAA
CATTCTTTGGGCCTCCTGGACTACAGGAGATGCTGTCACTTAATAATCAACCTGGGGTTC
GAAATCAGTGAGACCTGGATTCAAATTCTGCCTTGAAATATTGTGACTCTGGGAATGACA
ACACCTGGTTTGTTCTCTGTTGTATCCCCAGCCCCAAAGACAGCTCCTGGCCATATATCA
AGGTTTCAATAAATATTTGCTAAATGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAA

FIGURE 208

MRILQLILLALATGLVGGETRIIKGFECKPHSQPWQAALFEKTRLLCGATLIAPRWLLTA
AHCLKPRYIVHLGQHNLQKEEGCEQTRTATESFPHPGFNNSLPNKDHRNDIMLVKMASPV
SITWAVRPLTLSSRCVTAGTSCLISGWGSTSSPQLRLPHTLRCANITIIEHQKCENAYPG
NITDTMVCASVQEGGKDSCQGDSGGPLVCNQSLQGIISWGQDPCAITRKPGVYTKVCKYV
DWIQETMKNN

Important features:
Signal peptide:
amino acids 1-18

Serine proteases, trypsin family, histidine active site:
amino acids 58-63

N-glycosylation sites:
amino acids 99-102, 165-168, 181-184, 210-213

Glycosaminoglycan attachment site:
amino acids 145-148

Kringle domain proteins:
amino acids 197-209, 47-64

Serine proteases, trypsin family, histidine protein:
amino acids 199-209, 47-63, 220-243

Apple domain proteins:
amino acids 222-249, 189-222

FIGURE 209

GCGGCCACACGCAGCTAGCCGGAGCCCGGACCAGGCGCCTGTGCCTCCTCCTCGTCCCTC
GCCGCGTCCGCGAAGCCTGGAGCCGGCGGGAGCCCCGCGCTCGCC<u>ATG</u>TCGGGCGAGCTC
AGCAACAGGTTCCAAGGAGGGAAGGCGTTCGGCTTGCTCAAAGCCCGGCAGGAGAGGAGG
CTGGCCGAGATCAACCGGGAGTTTCTGTGTGACCAGAAGTACAGTGATGAAGAGAACCTT
CCAGAAAAGCTCACAGCCTTCAAAGAGAAGTACATGGAGTTTGACCTGAACAATGAAGGC
GAGATTGACCTGATGTCTTTAAAGAGGATGATGGAGAAGCTTGGTGTCCCCAAGACCCAC
CTGGAGATGAAGAAGATGATCTCAGAGGTGACAGGAGGGGTCAGTGACACTATATCCTAC
CGAGACTTTGTGAACATGATGCTGGGGAAACGGTCGGCTGTCCTCAAGTTAGTCATGATG
TTTGAAGGAAAAGCCAACGAGAGCAGCCCCAAGCCAGTTGGCCCCCCTCCAGAGAGAGAC
ATTGCTAGCCTGCCC<u>**TGA**</u>GGACCCCGCCTGGACTCCCCAGCCTTCCCACCCCATACCTCC
CTCCCGATCTTGCTGCCCTTCTTGACACACTGTGATCTCTCTCTCTCTCATTTGTTTGGT
CATTGAGGGTTTGTTTGTGTTTTCATCAATGTCTTTGTAAAGCACAAATTATCTGCCTTA
AAGGGGCTCTGGGTCGGGGAATCCTGAGCCTTGGGTCCCCTCCCTCTCTTCTTCCCTCCT
TCCCCGCTCCCTGTGCAGAAGGGCTGATATCAAACCAAAAACTAGAGGGGGCAGGGCCAG
GGCAGGGAGGCTTCCAGCCTGTGTTCCCCTCACTTGGAGGAACCAGCACTCTCCATCCTT
TCAGAAAGTCTCCAAGCCAAGTTCAGGCTCACTGACCTGGCTCTGACGAGGACCCCAGGC
CACTCTGAGAAGACCTTGGAGTAGGGACAAGGCTGCAGGGCCTCTTTCGGGTTTCCTTGG
ACAGTGCCATGGTTCCAGTGCTCTGGTGTCACCCAGGACACAGCCACTCGGGGCCCCGCT
GCCCCAGCTGATCCCCACTCATTCCACACCTCTTCTCATCCTCAGTGATGTGAAGGTGGG
AAGGAAAGGAGCTTGGCATTGGGAGCCCTTCAAGAAGGTACCAGAAGGAACCCTCCAGTC
CTGCTCTCTGGCCACACCTGTGCAGGCAGCTGAGAGGCAGCGTGCAGCCCTACTGTCCCT
TACTGGGGCAGCAGAGGGCTTCGGAGGCAGAAGTGAGGCCTGGGGTTTGGGGGGAAAGGT
CAGCTCAGTGCTGTTCCACCTTTTAGGGAGGATACTGAGGGGACCAGGATGGAGAATGA
GGAGTAAAATGCTCACGGCAAAGTCAGCAGCACTGGTAAGCCAAGACTGAGAAATACAAG
GTTGCTTGTCTGACCCCAATCTGCTTGAAAAAAAAAAAAAAAAA

FIGURE 210

MSGELSNRFQGGKAFGLLKARQERRLAEINREFLCDQKYSDEENLPEKLTAFKEKYMEFD
LNNEGEIDLMSLKRMMEKLGVPKTHLEMKKMISEVTGGVSDTISYRDFVNMMLGKRSAVL
KLVMMFEGKANESSPKPVGPPPERDIASLP

FIGURE 211

CTGGGATCAGCCACTGCAGCTCCCTGAGCACTCTCTACAGAGACGCGGACCCCAGACATG
AGGAGGCTCCTCCTGGTCACCAGCCTGGTGGTTGTGCTGCTGTGGGAGGCAGGTGCAGTC
CCAGCACCCAAGGTCCCTATCAAGATGCAAGTCAAACACTGGCCCTCAGAGCAGGACCCA
GAGAAGGCCTGGGGCGCCCGTGTGGTGGAGCCTCCGGAGAAGGACGACCAGCTGGTGGTG
CTGTTCCCTGTCCAGAAGCCGAAACTCTTGACCACCGAGGAGAAGCCACGAGGTCAGGGC
AGGGGCCCCATCCTTCCAGGCACCAAGGCCTGGATGGAGACCGAGGACACCCTGGGCCGT
GTCCTGAGTCCCGAGCCCGACCATGACAGCCTGTACCACCCTCCGCCTGAGGAGGACCAG
GGCGAGGAGAGGCCCCGGTTGTGGGTGATGCCAAATCACCAGGTGCTCCTGGGACCGGAG
GAAGACCAAGACCACATCTACCACCCCCAGTAGGGCTCCAGGGGCCATCACTGCCCCCGC
CCTGTCCCAAGGCCCAGGCTGTTGGGACTGGGACCCTCCCTACCCTGCCCCAGCTAGACA
AATAAACCCCAGCAGGCAAAAAAAAAAAAAAAAAA

FIGURE 212

MRRLLLVTSLVVVLLWEAGAVPAPKVPIKMQVKHWPSEQDPEKAWGARVVEPPEKDDQLV
VLFPVQKPKLLTTEEKPRGQGRGPILPGTKAWMETEDTLGRVLSPEPDHDSLYHPPPEED
QGEERPRLWVMPNHQVLLGPEEDQDHIYHPQ

FIGURE 213

CAGGCAGAAGCGAACAAAGACCCAGCAAGAGAAGGCAGAGGCTAAGACCCATCCCGTATC
TGCTCTCCTGAAATAATTCTGGAGTC**ATG**CCTGAAATGCCAGAGGACATGGAGCAGGAGG
AAGTTAACATCCCTAATAGGAGGGTTCTGGTTACTGGTGCCACTGGGCTTCTTGGCAGAG
CTGTACACAAAGAATTTCAGCAGAATAATTGGCATGCAGTTGGCTGTGGTTTCAGAAGAG
CAAGACCAAAATTTGAACAGGTTAATCTGTTGGATTCTAATGCAGTTCATCACATCATTC
ATGATTTTCAGCCCCATGTTATAGTACATTGTGCAGCAGAGAGAAGACCAGATGTTGTAG
AAAATCAGCCAGATGCTGCCTCTCAACTTAATGTGGATGCTTCTGGGAATTTAGCAAAGG
AAGCAGCTGCTGTTGGAGCATTTCTCATCTACATTAGCTCAGATTATGTATTTGATGGAA
CAAATCCACCTTACAGAGAGGAAGACATACCAGCTCCCCTAAATTTGTATGGCAAAACAA
AATTAGATGGAGAAAAGGCTGTCCTGGAGAACAATCTAGGAGCTGCTGTTTTGAGGATTC
CTATTCTGTATGGGGAAGTTGAAAAGCTCGAAGAAAGTGCTGTGACTGTTATGTTTGATA
AAGTGCAGTTCAGCAACAAGTCAGCAAACATGGATCACTGGCAGCAGAGGTTCCCCACAC
ATGTCAAAGATGTGGCCACTGTGTGCCGGCAGCTAGCAGAGAAGAGAATGCTGGATCCAT
CAATTAAGGGAACCTTTCACTGGTCTGGCAATGAACAGATGACTAAGTATGAAATGGCAT
GTGCAATTGCAGATGCCTTCAACCTCCCCAGCAGTCACTTAAGACCTATTACTGACAGCC
CTGTCCTAGGAGCACAACGTCCGAGAAATGCTCAGCTTGACTGCTCCAAATTGGAGACCT
TGGGCATTGGCCAACGAACACCATTTCGAATTGGAATCAAAGAATCACTTTGGCCTTTCC
TCATTGACAAGAGATGGAGACAAACGGTCTTTCAT**TAG**TTTATTTGTGTTGGGTTCTTTT
TTTTTTTAAATGAAAAGTATAGTATGTGGCACTTTTTAAAGAACAAAGGAAATAGTTTTG
TATGAGTACTTTAATTGTGACTCTTAGGATCTTTCAGGTAAATGATGCTCTTGCACTAGT
GAAATTGTCTAAAGAAACTAAAGGGCAGTCATGCCCTGTTTGCAGTAATTTTTCTTTTTA
TCATTTTGTTTGTCCTGGCTAAACTTGGAGTTTGAGTATAGTAAATTATGATCCTTAAAT
ATTTGAGAGTCAGGATGAAGCAGATCTGCTGTAGACTTTTCAGATGAAATTGTTCATTCT
CGTAACCTCCATATTTTCAGGATTTTTGAAGCTGTTGACCTTTTCATGTTGATTATTTTA
AATTGTGTGAAATAGTATAAAAATCATTGGTGTTCATTATTTGCTTTGCCTGAGCTCAGA
TCAAAATGTTTGAAGAAAGGAACTTTATTTTTGCAAGTTACGTACAGTTTTTATGCTTGA
GATATTTCAACATGTTATGTATATTGGAACTTCTACAGCTTGATGCCTCCTGCTTTTATA
GCAGTTTATGGGGAGCACTTGAAAGAGCGTGTGTACATGTATTTTTTTTCTAGGCAAACA
TTGAATGCAAACGTGTATTTTTTTAATATAAATATATAACTGTCCTTTTCATCCCATGTT
GCCGCTAAGTGATATTTCATATGTGTGGTTATACTCATAATAATGGGCCTTGTAAGTCTT
TTCACCATTCATGAATAATAATAAATATGTACTGCTGGCATGTAATGCTTAGTTTTCTTG
TATTTACTTCTTTTTTTTAAATGTAAGGACCAAACTTCTAAACTAATTGTTCTTTTGTTGC
TTTAATTTTTAAAAATTACATTCTTCTGATGTAACATGTGATACATACAAAAGAATATAG
TTTAATATGTATTGAAATAAAACACAATAAAATT

FIGURE 214

MPEMPEDMEQEEVNIPNRRVLVTGATGLLGRAVHKEFQQNNWHAVGCGFRRARPKFEQVN
LLDSNAVHHIIHDFQPHVIVHCAAERRPDVVENQPDAASQLNVDASGNLAKEAAAVGAFL
IYISSDYVFDGTNPPYREEDIPAPLNLYGKTKLDGEKAVLENNLGAAVLRIPILYGEVEK
LEESAVTVMFDKVQFSNKSANMDHWQQRFPTHVKDVATVCRQLAEKRMLDPSIKGTFHWS
GNEQMTKYEMACAIADAFNLPSSHLRPITDSPVLGAQRPRNAQLDCSKLETLGIGQRTPF
RIGIKESLWPFLIDKRWRQTVFH

Signal peptide:
amino acids 1-30

Transmembrane domain:
amino acids 105-127

N-glycosylation site:
amino acids 197-201

N-myristoylation site:
amino acids 303-309

Short-chain dehydrogenases/reductases family proteins:
amino acids 18-30

FIGURE 215

GTGAATGTGAGGGTTTGATGACTTTCAGATGTCTAGGAACCAGAGTGGGTGCAGGGGCCC
CAGGCAGGGCTGATTCTTGGGCGGAGGAGAGTAGGGTAAAGGGTTCTGCATGAGCTCCTT
AAAGGACAAAGGTAACAGAGCCAGCGAGAGAGCTCGAGGGGAGACTTTGACTTCAAGCCA
CAGAATTGGTGGAAGTGTGCGCGCCGCCGCCGCCGTCGCTCCTGCAGCGCTGTCGACCTA
GCCGCTAGCATCTTCCCGAGCACCGGGATCCCGGGGTAGGAGGCGACGCGGGCGAGCACC
AGCGCCAGCCGGCTGCGGCTGCCCACACGGCTCACC**ATG**GGCTCCGGGCGCCGGGCGCTG
TCCGCGGTGCCGGCCGTGCTGCTGGTCCTCACGCTGCCGGGGCTGCCCGTCTGGGCACAG
AACGACACGGAGCCCATCGTGCTGGAGGGCAAGTGTCTGGTGGTGTGCGACTCGAACCCG
GCCACGGACTCCAAGGGCTCCTCTTCCTCCCCGCTGGGGATATCGGTCCGGGCGGCCAAC
TCCAAGGTCGCCTTCTCGGCGGTGCGGAGCACCAACCACGAGCCATCCGAGATGAGCAAC
AAGACGCGCATCATTTACTTCGATCAGATCCTGGTGAATGTGGGTAATTTTTTCACATTG
GAGTCTGTCTTTGTAGCACCAAGAAAAGGAATTTACAGTTTCAGTTTTCACGTGATTAAA
GTCTACCAGAGCCAAACTATCCAGGTTAACTTGATGTTAAATGGAAAACCAGTAATATCT
GCCTTTGCGGGGGACAAAGATGTTACTCGTGAAGCTGCCACGAATGGTGTCCTGCTCTAC
CTAGATAAAGAGGATAAGGTTTACCTAAAACTGGAGAAAGGTAATTTGGTTGGAGGCTGG
CAGTATTCCACGTTTTCTGGCTTTCTGGTGTTCCCCCTA**TAG**GATTCAATTTCTCCATGA
TGTTCATCCAGGTGAGGGATGACCCACTCCTGAGTTATTGGAAGATCATTTTTTCATCAT
TGGATTGATGTCTTTTATTGGTTTCTCATGGGTGGATATGGATTCTAAGGATTCTAGCCT
GTCTGAACCAATACAAAATTTCACAGATTATTTGTGTGTGTCTGTTTCAGTATATTTGGA
TTGGGACTCTAAGCAGATAATACCTATGCTTAAATGTAACAGTCAAAAGCTGTCTGCAAG
ACTTATTCTGAATTTCATTTCCTGGGATTACTGAATTAGTTACAGATGTGGAATTTTATT
TGTTTAGTTTTAAAAGACTGGCAACCAGGTCTAAGGATTAGAAAACTCTAAAGTTCTGAC
TTCAATCAACGGTTAGTGTGATACTGCCAAAGAACTGTATACTGTGTTAATATATTGATT
ATATTTGTTTTTATTCCTTTGGAATTAGTTTGTTTGGTTCTTGTAAAAAACTTGGATTTT
TTTTTTCAGTAACTGGTATTATGTTTTCTCTTAAAATAAGGTAATGAATGGCTTGCCCAC
AAATTTACCTTGACTACGATATCATCGACATGACTTCTCTCAAAAAAAAAGAATGCTTCA
TAGTTGTATTTTAATTGTATATGTGAAAGAGTCATATTTTCCAAGTTATATTTTCTAAGA
AGAAGAATAGATCATAAATCTGACAAGGAAAAAGTTGCTTACCCAAAATCTAAGTGCTCA
ATCCCTGAGCCTCAGCAAAACAGCTCCCCTCCGAGGGAAATCTTATACTTTATTGCTCAA
CTTTAATTAAAATGATTGATAATAACCACTTTATTAAAAACCTAAGGTTTTTTTTTTTTC
CGTAGACATGACCACTTTATTAACTGGTGGTGGGATGCTGTTGTTTCTAATTATACCTAT
TTTTCAAGGCTTCTGTTGTATTTGAAGTATCATCTGGTTTTGCCTTAACTCTTTAAATTG
TATATATTTATCTGTTTAGCTAATATTAAATTCAAATATCCCATATCTAAATTTAGTGCA
ATATCTTGTCTTTTGTATAGGTCATATGAATTCATAAAATTATTTATGTCTGTTATAGAA
TAAAGATTAATATATGTTAAAAAAA

FIGURE 216

MGSGRRALSAVPAVLLVLTLPGLPVWAQNDTEPIVLEGKCLVVCDSNPATDSKGSSSSPL
GISVRAANSKVAFSAVRSTNHEPSEMSNKTRIIYFDQILVNVGNFFTLESVFVAPRKGIY
SFSFHVIKVYQSQTIQVNLMLNGKPVISAFAGDKDVTREAATNGVLLYLDKEDKVYLKLE
KGNLVGGWQYSTFSGFLVFPL

Signal peptide:
amino acids 1-27

FIGURE 217

CGGCAACCAGCCGCCGCCACCACCGCTGCCACTGCCGCCCTGCCGGGGCC**ATG**TTCGCTC
TGGGCTTGCCCTTCTTGGTGCTCTTGGTGGCCTCGGTCGAGAGCCATCTGGGGGTTCTGG
GGCCCAAGAACGTCTCGCAGAAAGACGCCGAGTTTGAGCGCACCTACGTGGACGAGGTCA
ACAGCGAGCTGGTCAACATCTACACCTTCAACCATACTGTGACCCGCAACAGGACAGAGG
GCGTGCGTGTGTCTGTGAACGTCCTGAACAAGCAGAAGGGGGCGCCGTTGCTGTTTGTGG
TCCGCCAGAAGGAGGCTGTGGTGTCCTTCCAGGTGCCCCTAATCCTGCGAGGGATGTTTC
AGCGCAAGTACCTCTACCAAAAAGTGGAACGAACCCTGTGTCAGCCCCCCACCAAGAATG
AGTCGGAGATTCAGTTCTTCTACGTGGATGTGTCCACCCTGTCACCAGTCAACACCACAT
ACCAGCTCCGGGTCAGCCGCATGGACGATTTTGTGCTCAGGACTGGGGAGCAGTTCAGCT
TCAATACCACAGCAGCACAGCCCCAGTACTTCAAGTATGAGTTCCCTGAAGGCGTGGACT
CGGTAATTGTCAAGGTGACCTCCAACAAGGCCTTCCCCTGCTCAGTCATCTCCATTCAGG
ATGTGCTGTGTCCTGTCTATGACCTGGACAACAACGTAGCCTTCATCGGCATGTACCAGA
CGATGACCAAGAAGGCGGCCATCACCGTACAGCGCAAAGACTTCCCCAGCAACAGCTTTT
ATGTGGTGGTGGTGGTGAAGACCGAAGACCAAGCCTGCGGGGGCTCCCTGCCTTTCTACC
CCTTCGCAGAAGATGAACCGGTCGATCAAGGGCACCGCCAGAAAACCCTGTCAGTGCTGG
TGTCTCAAGCAGTCACGTCTGAGGCATACGTCAGTGGGATGCTCTTTTGCCTGGGTATAT
TTCTCTCCTTTTACCTGCTGACCGTCCTCCTGGCCTGCTGGGAGAACTGGAGGCAGAAGA
AGAAGACCCTGCTGGTGGCCATTGACCGAGCCTGCCCAGAAAGCGGTCACCCTCGAGTCC
TGGCTGATTCTTTTCCTGGCAGTTCCCCTTATGAGGGTTACAACTATGGCTCCTTTGAGA
ATGTTTCTGGATCTACCGATGGTCTGGTTGACAGCGCTGGCACTGGGGACCTCTCTTACG
GTTACCAGGGCCGCTCCTTTGAACCTGTAGGTACTCGGCCCCGAGTGGACTCCATGAGCT
CTGTGGAGGAGGATGACTACGACACATTGACCGACATCGATTCCGACAAGAATGTCATTC
GCACCAAGCAATACCTCTATGTGGCTGACCTGGCACGGAAGGACAAGCGTGTTCTGCGGA
AAAAGTACCAGATCTACTTCTGGAACATTGCCACCATTGCTGTCTTCTATGCCCTTCCTG
TGGTGCAGCTGGTGATCACCTACCAGACGGTGGTGAATGTCACAGGGAATCAGGACATCT
GCTACTACAACTTCCTCTGCGCCCACCCACTGGGCAATCTCAGCGCCTTCAACAACATCC
TCAGCAACCTGGGGTACATCCTGCTGGGGCTGCTTTTCCTGCTCATCATCCTGCAACGGG
AGATCAACCACAACCGGGCCCTGCTGCGCAATGACCTCTGTGCCCTGGAATGTGGGATCC
CCAAACACTTTGGGCTTTTCTACGCCATGGGCACAGCCCTGATGATGGAGGGGCTGCTCA
GTGCTTGCTATCATGTGTGCCCCAACTATACCAATTTCCAGTTTGACACATCGTTCATGT
ACATGATCGCCGGACTCTGCATGCTGAAGCTCTACCAGAAGCGGCACCCGGACATCAACG
CCAGCGCCTACAGTGCCTACGCCTGCCTGGCCATTGTCATCTTCTTCTCTGTGCTGGGCG
TGGTCTTTGGCAAAGGGAACACGGCGTTCTGGATCGTCTTCTCCATCATTCACATCATCG
CCACCCTGCTCCTCAGCACGCAGCTCTATTACATGGGCCGGTGGAAACTGGACTCGGGGA
TCTTCCGCCGCATCCTCCACGTGCTCTACACAGACTGCATCCGGCAGTGCAGCGGGCCGC
TCTACGTGGACCGCATGGTGCTGCTGGTCATGGGCAACGTCATCAACTGGTCGCTGGCTG
CCTATGGGCTTATCATGCGCCCCAATGATTTCGCTTCCTACTTGTTGGCCATTGGCATCT
GCAACCTGCTCCTTTACTTCGCCTTCTACATCATCATGAAGCTCCGGAGTGGGGAGAGGA
TCAAGCTCATCCCCCTGCTCTGCATCGTTTGCACCTCCGTGGTCTGGGGCTTCGCGCTCT
TCTTCTTCTTCCAGGGACTCAGCACCTGGCAGAAAACCCCTGCAGAGTCGAGGGAGCACA
ACCGGGACTGCATCCTCCTCGACTTCTTTGACGACCACGACATCTGGCACTTCCTCTCCT
CCATCGCCATGTTCGGGTCCTTCCTGGTGTTGCTGACACTGGATGACGACCTGGATACTG
TGCAGCGGGACAAGATCTATGTCTTC**TAG**CAGGAGCTGGGCCCTTCGCTTCACCTCAAGG
GGCCCTGAGCTCCTTTGTGTCATAGACCGGTCACTCTGTCGTGCTGTGGGGATGAGTCCC
AGCACCGCTGCCCAGCACTGGATGGCAGCAGGACAGCCAGGTCTAGCTTAGGCTTGGCCT
GGGACAGCCATGGGGTGGCATGGAACCTTGCAGCTGCCCTCTGCCGAGGAGCAGGCCTGC
TCCCCTGGAACCCCCAGATGTTGGCCAAATTGCTGCTTTCTTCTCAGTGTTGGGGCCTTC

CATGGGCCCCTGTCCTTTGGCTCTCCATTTGTCCCTTTGCAAGAGGAAGGATGGAAGGGA
CACCCTCCCCATTTCATGCCTTGCATTTTGCCCGTCCTCCTCCCCACAATGCCCCAGCCT
GGGACCTAAGGCCTCTTTTTCCTCCCATACTCCCACTCCAGGGCCTAGTCTGGGGCCTGA
ATCTCTGTCCTGTATCAGGGCCCCAGTTCTCTTTGGGCTGTCCCTGGCTGCCATCACTGC
CCATTCCAGTCAGCCAGGATGGATGGGGGTATGAGATTTTGGGGGTTGGCCAGCTGGTGC
CAGACTTTTGGTGCTAAGGCCTGCAAGGGGCCTGGGGCAGTGCGTATTCTCTTCCCTCTG
ACCTGTGCTCAGGGCTGGCTCTTTAGCAATGCGCTCAGCCCAATTTGAGAACCGCCTTCT
GATTCAAGAGGCTGAATTCAGAGGTCACCTCTTCATCCCATCAGCTCCCAGACTGATGCC
AGCACCAGGACTGGAGGGAGAAGCGCCTCACCCCTTCCCTTCCTTCTTTCCAGGCCCTTA
GTCTTGCCAAACCCCAGCTGGTGGCCTTTCAGTGCCATTGACACTGCCCAAGAATGTCCA
GGGGCAAAGGAGGGATGATACAGAGTTCAGCCCGTTCTGCCTCCACAGCTGTGGGCACCC
CAGTGCCTACCTTAGAAAGGGGCTTCAGGAAGGGATGTGCTGTTTCCCTCTACGTGCCCA
GTCCTAGCCTCGCTCTAGGACCCAGGGCTGGCTTCTAAGTTTCCGTCCAGTCTTCAGGCA
AGTTCTGTGTTAGTCATGCACACACATACCTATGAAACCTTGGAGTTTACAAAGAATTGC
CCCAGCTCTGGGCACCCTGGCCACCCTGGTCCTTGGATCCCCTTCGTCCCACCTGGTCCA
CCCCAGATGCTGAGGATGGGGGAGCTCAGGCGGGGCCTCTGCTTTGGGGATGGGAATGTG
TTTTTCTCCCAAACTTGTTTTTATAGCTCTGCTTGAAGGGCTGGGAGATGAGGTGGGTCT
GGATCTTTTCTCAGAGCGTCTCCATGCTATGGTTGCATTTCCGTTTTCTATGAATGAATT
TGCATTCAATAAACAACCAGACTCAAAAAAAAAAAAAAA

FIGURE 218

MFALGLPFLVLLVASVESHLGVLGPKNVSQKDAEFERTYVDEVNSELVNIYTFNHTVTRN
RTEGVRVSVNVLNKQKGAPLLFVVRQKEAVVSFQVPLILRGMFQRKYLYQKVERTLCQPP
TKNESEIQFFYVDVSTLSPVNTTYQLRVSRMDDFVLRTGEQFSFNTTAAQPQYFKYEFPE
GVDSVIVKVTSNKAFPCSVISIQDVLCPVYDLDNNVAFIGMYQTMTKKAAITVQRKDFPS
NSFYVVVVVKTEDQACGGSLPFYPFAEDEPVDQGHRQKTLSVLVSQAVTSEAYVSGMLFC
LGIFLSFYLLTVLLACWENWRQKKKTLLVAIDRACPESGHPRVLADSFPGSSPYEGYNYG
SFENVSGSTDGLVDSAGTGDLSYGYQGRSFEPVGTRPRVDSMSSVEEDDYDTLTDIDSDK
NVIRTKQYLYVADLARKDKRVLRKKYQIYFWNIATIAVFYALPVVQLVITYQTVVNVTGN
QDICYYNFLCAHPLGNLSAFNNILSNLGYILLGLLFLLIILQREINHNRALLRNDLCALE
CGIPKHFGLFYAMGTALMMEGLLSACYHVCPNYTNFQFDTSFMYMIAGLCMLKLYQKRHP
DINASAYSAYACLAIVIFFSVLGVVFGKGNTAFWIVFSIIHIIATLLLSTQLYYMGRWKL
DSGIFRRILHVLYTDCIRQCSGPLYVDRMVLLVMGNVINWSLAAYGLIMRPNDFASYLLA
IGICNLLLYFAFYIIMKLRSGERIKLIPLLCIVCTSVVWGFALFFFFQGLSTWQKTPAES
REHNRDCILLDFFDDHDIWHFLSSIAMFGSFLVLLTLDDDLDTVQRDKIYVF

Important features of the protein:
Signal peptide:
amino acids 1-18

Transmembrane domains:
amino acids 292-317, 451-470, 501-520, 607-627, 751-770

Leucine zipper pattern:
amino acids 497-518

N-glycosylation sites:
amino acids 27-30, 54-57, 60-63, 123-126, 141-144, 165-168, 364-367, 476-479, 496-499, 572-575, 603-606, 699-702

FIGURE 219

AATTTTTCACCAGAGTAAACTTGAGAAACCAACTGGACCTTGAGTATTGTACATTTTGCC
TCGTGGACCCAAAGGTAGCAATCTGAAACATGAGGAGTACGATTCTACTGTTTTGTCTTC
TAGGATCAACTCGGTCATTACCACAGCTCAAACCTGCTTTGGGACTCCCTCCCACAAAAC
TGGCTCCGGATCAGGGAACACTACCAAACCAACAGCAGTCAAATCAGGTCTTTCCTTCTT
TAAGTCTGATACCATTAACACAGATGCTCACACTGGGGCCAGATCTGCATCTGTTAAATC
CTGCTGCAGGAATGACACCTGGTACCCAGACCCACCCATTGACCCTGGGAGGGTTGAATG
TACAACAGCAACTGCACCCACATGTGTTACCAATTTTTGTCACACAACTTGGAGCCCAGG
GCACTATCCTAAGCTCAGAGGAATTGCCACAAATCTTCACGAGCCTCATCATCCATTCCT
TGTTCCCGGGAGGCATCCTGCCCACCAGTCAGGCAGGGGCTAATCCAGATGTCCAGGATG
GAAGCCTTCCAGCAGGAGGAGCAGGTGTAAATCCTGCCACCCAGGGAACCCCAGCAGGCC
GCCTCCCAACTCCCAGTGGCACAGATGACGACTTTGCAGTGACCACCCCTGCAGGCATCC
AAAGGAGCACACATGCCATCGAGGAAGCCACCACAGAATCAGCAAATGGAATTCAGTAAG
CTGTTTCAAATTTTTTCAACTAAGCTGCCTCGAATTTGGTGATACATGTGAATCTTTATC
ATTGATTATATTATGGAATAGATTGAGACACATTGGATAGTCTTAGAAGAAATTAATTCT
TAATTTACCTGAAAATATTCTTGAAATTTCAGAAAATATGTTCTATGTAGAGAATCCCAA
CTTTTAAAAACAATAATTCAATGGATAAATCTGTCTTTGAAATATAACATTATGCTGCCT
GGATGATATGCATATTAAAACATATTTGGAAAACTGGAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 220

MRSTILLFCLLGSTRSLPQLKPALGLPPTKLAPDQGTLPNQQQSNQVFPSLSLIPLTQML
TLGPDLHLLNPAAGMTPGTQTHPLTLGGLNVQQQLHPHVLPIFVTQLGAQGTILSSEELP
QIFTSLIIHSLFPGGILPTSQAGANPDVQDGSLPAGGAGVNPATQGTPAGRLPTPSGTDD
DFAVTTPAGIQRSTHAIEEATTESANGIQ

Signal peptide:
amino acids 1-16

FIGURE 221

GACTTTGCTTGAATGTTTACATTTTCTGCTCGCTGTCCTACATATCACAATATAGTGTTC
ACGTTTTGTTAAAACTTTGGGGTGTCAGGAGTTGAGCTTGCTCAGCAAGCCAGC**ATG**GCT
AGGATGAGCTTTGTTATAGCAGCTTGCCAATTGGTGCTGGGCCTACTAATGACTTCATTA
ACCGAGTCTTCCATACAGAATAGTGAGTGTCCACAACTTTGCGTATGTGAAATTCGTCCC
TGGTTTACCCCACAGTCAACTTACAGAGAAGCCACCACTGTTGATTGCAATGACCTCCGC
TTAACAAGGATTCCCAGTAACCTCTCTAGTGACACACAAGTGCTTCTCTTACAGAGCAAT
AACATCGCGAAGACTGTGGATGAGCTGCAGCAGCTTTTCAACTTGACTGAACTAGATTTC
TCCCAAAACAACTTTACTAACATTAAGGAGGTCGGGCTGGCAAACCTAACCCAGCTCACA
ACGCTGCATTTGGAGGAAAATCAGATTACCGAGATGACTGATTACTGTCTACAAGACCTC
AGCAACCTTCAAGAACTCTACATCAACCACAACCAAATTAGCACTATTTCTGCTCATGCT
TTTGCAGGCTTAAAAAATCTATTAAGGCTCCACCTGAACTCCAACAAATTGAAAGTTATT
GATAGTCGCTGGTTTGATTCTACACCCAACCTGGAAATTCTCATGATCGGAGAAAACCCT
GTGATTGGAATTCTGGATATGAACTTCAAACCCCTCGCAAATTTGAGAAGCTTAGTTTTG
GCAGGAATGTATCTCACTGATATTCCTGGAAATGCTTTGGTGGGTCTGGATAGCCTTGAG
AGCCTGTCTTTTTATGATAACAAACTGGTTAAAGTCCCTCAACTTGCCCTGCAAAAAGTT
CCAAATTTGAAATTCTTAGACCTCAACAAAAACCCCATTCACAAAATCCAAGAAGGGGAC
TTCAAAAATATGCTTCGGTTAAAAGAACTGGGAATCAACAATATGGGCGAGCTCGTTTCT
GTCGACCGCTATGCCCTGGATAACTTGCCTGAACTCACAAAGCTGGAAGCCACCAATAAC
CCTAAACTCTCTTACATCCACCGCTTGGCTTTCCGAAGTGTCCCTGCTCTGGAAAGCTTG
ATGCTGAACAACAATGCCTTGAATGCCATTTACCAAAAGACAGTCGAATCCCTCCCCAAT
CTGCGTGAGATCAGTATCCATAGCAATCCCCTCAGGTGTGACTGTGTGATCCACTGGATT
AACTCCAACAAAACCAACATCCGCTTCATGGAGCCCCTGTCCATGTTCTGTGCCATGCCG
CCCGAATATAAAGGGCACCAGGTGAAGGAAGTTTTAATCCAGGATTCGAGTGAACAGTGC
CTCCCAATGATATCTCACGACAGCTTCCCAAATCGTTTAAACGTGGATATCGGCACGACG
GTTTTCCTAGACTGTCGAGCCATGGCTGAGCCAGAACCTGAAATTTACTGGGTCACTCCC
ATTGGAAATAAGATAACTGTGGAAACCCTTTCAGATAAATACAAGCTAAGTAGCGAAGGT
ACCTTGGAAATATCTAACATACAAATTGAAGACTCAGGAAGATACACATGTGTTGCCCAG
AATGTCCAAGGGGCAGACACTCGGGTGGCAACAATTAAGGTTAACGGGACCCTTCTGGAT
GGTACCCAGGTGCTAAAAATATACGTCAAGCAGACAGAATCCCATTCCATCTTAGTGTCC
TGGAAAGTTAATTCCAATGTCATGACGTCAAACTTAAAATGGTCGTCTGCCACCATGAAG
ATTGATAACCCTCACATAACATATACTGCCAGGGTCCCAGTCGATGTCCATGAATACAAC
CTAACGCATCTGCAGCCTTCCACAGATTATGAAGTGTGTCTCACAGTGTCCAATATTCAT
CAGCAGACTCAAAAGTCATGCGTAAATGTCACAACCAAAAATGCCGCCTTCGCAGTGGAC
ATCTCTGATCAAGAAACCAGTACAGCCCTTGCTGCAGTAATGGGGTCTATGTTTGCCGTC
ATTAGCCTTGCGTCCATTGCTGTGTACTTTGCCAAAAGATTTAAGAGAAAAAACTACCAC
CACTCATTAAAAAAGTATATGCAAAAAACCTCTTCAATCCCACTAAATGAGCTGTACCCA
CCACTCATTAACCTCTGGGAAGGTGACAGCGAGAAAGACAAAGATGGTTCTGCAGACACC
AAGCCAACCCAGGTCGACACATCCAGAAGCTATTACATGTGG**TAA**CTCAGAGGATATTTT
GCTTCTGGTAGTAAGGAGCACAAAGACGTTTTTGCTTTATTCTGCAAAAGTGAACAAGTT
GAAGACTTTTGTATTTTTGACTTTGCTAGTTTGTGGCAGAGTGGAGAGGACGGGTGGATA
TTTCAAATTTTTTTAGTATAGCGTATCGCAAGGGTTTGACACGGCTGCCAGCGACTCTAG
GCTTCCAGTCTGTGTTTGGTTTTTATTCTTATCATTATTATGATTGTTATTATATTATTA
TTTTATTTTAGTTGTTGTGCTAAACTCAATAATGCTGTTCTAACTACAGTGCTCAATAAA
ATGATTAATGACAGGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 222

MARMSFVIAACQLVLGLLMTSLTESSIQNSECPQLCVCEIRPWFTPQSTYREATTVDCND
LRLTRIPSNLSSDTQVLLLQSNNIAKTVDELQQLFNLTELDFSQNNFTNIKEVGLANLTQ
LTTLHLEENQITEMTDYCLQDLSNLQELYINHNQISTISAHAFAGLKNLLRLHLNSNKLK
VIDSRWFDSTPNLEILMIGENPVIGILDMNFKPLANLRSLVLAGMYLTDIPGNALVGLDS
LESLSFYDNKLVKVPQLALQKVPNLKFLDLNKNPIHKIQEGDFKNMLRLKELGINNMGEL
VSVDRYALDNLPELTKLEATNNPKLSYIHRLAFRSVPALESLMLNNNALNAIYQKTVESL
PNLREISIHSNPLRCDCVIHWINSNKTNIRFMEPLSMFCAMPPEYKGHQVKEVLIQDSSE
QCLPMISHDSFPNRLNVDIGTTVFLDCRAMAEPEPEIYWVTPIGNKITVETLSDKYKLSS
EGTLEISNIQIEDSGRYTCVAQNVQGADTRVATIKVNGTLLDGTQVLKIYVKQTESHSIL
VSWKVNSNVMTSNLKWSSATMKIDNPHITYTARVPVDVHEYNLTHLQPSTDYEVCLTVSN
IHQQTQKSCVNVTTKNAAFAVDISDQETSTALAAVMGSMFAVISLASIAVYFAKRFKRKN
YHHSLKKYMQKTSSIPLNELYPPLINLWEGDSEKDKDGSADTKPTQVDTSRSYYMW

Important features:
Signal peptide:
Amino acids 1-25

Transmembrane domain:
Amino acids 508-530

N-glycosylation sites:
Amino acids 69-73;96-100;106-110;117-121;385-389;517-521;
582-586;611-615

Tyrosine kinase phosphorylation site:
Amino acids 573-582

N-myristoylation sites:
Amino acids 16-22;224-230;464-470;637-643;698-704

FIGURE 223

CAACCATGCAAGGACAGGGCAGGAGAAGAGGAACCTGCAAAGACATATTTTGTTCCAAA**A**
TGGCATCTTACCTTTATGGAGTACTCTTTGCTGTTGGCCTCTGTGCTCCAATCTACTGTG
TGTCCCCGGCCAATGCCCCCAGTGCATACCCCCGCCCTTCCTCCACAAAGAGCACCCCTG
CCTCACAGGTGTATTCCCTCAACACCGACTTTGCCTTCCGCCTATACCGCAGGCTGGTTT
TGGAGACCCCGAGTCAGAACATCTTCTTCTCCCCTGTGAGTGTCTCCACTTCCCTGGCCA
TGCTCTCCCTTGGGGCCCACTCAGTCACCAAGACCCAGATTCTCCAGGGCCTGGGCTTCA
ACCTCACACACACACCAGAGTCTGCCATCCACCAGGGCTTCCAGCACCTGGTTCACTCAC
TGACTGTTCCCAGCAAAGACCTGACCTTGAAGATGGGAAGTGCCCTCTTCGTCAAGAAGG
AGCTGCAGCTGCAGGCAAATTTCTTGGGCAATGTCAAGAGGCTGTATGAAGCAGAAGTCT
TTTCTACAGATTTCTCCAACCCCTCCATTGCCCAGGCGAGGATCAACAGCCATGTGAAAA
AGAAGACCCAAGGGAAGGTTGTAGACATAATCCAAGGCCTTGACCTTCTGACGGCCATGG
TTCTGGTGAATCACATTTTCTTTAAAGCCAAGTGGGAGAAGCCCTTTCACCTTGAATATA
CAAGAAAGAACTTCCCATTCCTGGTGGGCGAGCAGGTCACTGTGCAAGTCCCCATGATGC
ACCAGAAAGAGCAGTTCGCTTTTGGGGTGGATACAGAGCTGAACTGCTTTGTGCTGCAGA
TGGATTACAAGGGAGATGCCGTGGCCTTCTTTGTCCTCCCTAGCAAGGGCAAGATGAGGC
AACTGGAACAGGCCTTGTCAGCCAGAACACTGATAAAGTGGAGCCACTCACTCCAGAAAA
GGTGGATAGAGGTGTTCATCCCCAGATTTTCCATTTCTGCCTCCTACAATCTGGAAACCA
TCCTCCCGAAGATGGGCATCCAAAATGCCTTTGACAAAAATGCTGATTTTTCTGGAATTG
CAAAGAGAGACTCCCTGCAGGTTTCTAAAGCAACCCACAAGGCTGTGCTGGATGTCAGTG
AAGAGGGCACTGAGGCCACAGCAGCTACCACCACCAAGTTCATAGTCCGATCGAAGGATG
GTCCCTCTTACTTCACTGTCTCCTTCAATAGGACCTTCCTGATGATGATTACAAATAAAG
CCACAGACGGTATTCTCTTTCTAGGGAAAGTGGAAAATCCCACTAAATCC**TAG**GTGGGAA
ATGGCCTGTTAACTGATGGCACATTGCTAATGCACAAGAAATAACAAACCACATCCCTCT
TTCTGTTCTGAGGGTGCATTTGACCCCAGTGGAGCTGGATTCGCTGGCAGGGATGCCACT
TCCAAGGCTCAATCACCAAACCATCAACAGGGACCCCAGTCACAAGCCAACACCCATTAA
CCCCAGTCAGTGCCCTTTTCCACAAATTCTCCCAGGTAACTAGCTTCATGGGATGTTGCT
GGGTTACCATATTTCCATTCCTTGGGGCTCCCAGGAATGGAAATACGCCAACCCAGGTTA
GGCACCTCTATTGCAGAATTACAATAACACATTCAATAAAACTAAAATATGAATTCAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAA

FIGURE 224

MASYLYGVLFAVGLCAPIYCVSPANAPSAYPRPSSTKSTPASQVYSLNTDFAFRLYRRLV
LETPSQNIFFSPVSVSTSLAMLSLGAHSVTKTQILQGLGFNLTHTPESAIHQGFQHLVHS
LTVPSKDLTLKMGSALFVKKELQLQANFLGNVKRLYEAEVFSTDFSNPSIAQARINSHVK
KKTQGKVVDIIQGLDLLTAMVLVNHIFFKAKWEKPFHLEYTRKNFPFLVGEQVTVQVPMM
HQKEQFAFGVDTELNCFVLQMDYKGDAVAFFVLPSKGKMRQLEQALSARTLIKWSHSLQK
RWIEVFIPRFSISASYNLETILPKMGIQNAFDKNADFSGIAKRDSLQVSKATHKAVLDVS
EEGTEATAATTTKFIVRSKDGPSYFTVSFNRTFLMMITNKATDGILFLGKVENPTKS

Signal peptide:
amino acids 1-20

FIGURE 225

GGGAGAGAGGATAAATAGCAGCGTGGCTTCCCTGGCTCCTCTCTGCATCCTTCCCGACCT
TCCCAGCAAT**ATG**CATCTTGCACGTCTGGTCGGCTCCTGCTCCCTCCTTCTGCTACTGGG
GGCCCTGTCTGGATGGGCGGCCAGCGATGACCCCATTGAGAAGGTCATTGAAGGGATCAA
CCGAGGGCTGAGCAATGCAGAGAGAGAGGTGGGCAAGGCCCTGGATGGCATCAACAGTGG
AATCACGCATGCCGGAAGGGAAGTGGAGAAGGTTTTCAACGGACTTAGCAACATGGGGAG
CCACACCGGCAAGGAGTTGGACAAAGGCGTCCAGGGGCTCAACCACGGCATGGACAAGGT
TGCCCATGAGATCAACCATGGTATTGGACAAGCAGGAAAGGAAGCAGAGAAGCTTGGCCA
TGGGGTCAACAACGCTGCTGGACAGGCCGGGAAGGAAGCAGACAAAGCGGTCCAAGGGTT
CCACACTGGGGTCCACCAGGCTGGGAAGGAAGCAGAGAAACTTGGCCAAGGGGTCAACCA
TGCTGCTGACCAGGCTGGAAAGGAAGTGGAGAAGCTTGGCCAAGGTGCCCACCATGCTGC
TGGCCAGGCCGGGAAGGAGCTGCAGAATGCTCATAATGGGGTCAACCAAGCCAGCAAGGA
GGCCAACCAGCTGCTGAATGGCAACCATCAAAGCGGATCTTCCAGCCATCAAGGAGGGGC
CACAACCACGCCGTTAGCCTCTGGGGCCTCAGTCAACACGCCTTTCATCAACCTTCCCGC
CCTGTGGAGGAGCGTCGCCAACATCATGCCC**TAA**ACTGGCATCCGGCCTTGCTGGGAGAA
TAATGTCGCCGTTGTCACATCAGCTGACATGACCTGGAGGGGTTGGGGGTGGGGGACAGG
TTTCTGAAATCCCTGAAGGGGGTTGTACTGGGATTTGTGAATAAACTTGATACACCA

FIGURE 226

MHLARLVGSCSLLLLLGALSGWAASDDPIEKVIEGINRGLSNAEREVGKALDGINSGITH
AGREVEKVFNGLSNMGSHTGKELDKGVQGLNHGMDKVAHEINHGIGQAGKEAEKLGHGVN
NAAGQAGKEADKAVQGFHTGVHQAGKEAEKLGQGVNHAADQAGKEVEKLGQGAHHAAGQA
GKELQNAHNGVNQASKEANQLLNGNHQSGSSSHQGGATTTPLASGASVNTPFINLPALWR
SVANIMP

Important features of the protein:
Signal peptide:
amino acids 1-25

Homologous region to circumsporozoite (CS) repeats:
amino acids 35-225

FIGURE 227

GAAGTAGAGGTGTTGTGCTGAGCGGCGCTCGGCGAACTGTGTGGACCGTCTGCTGGGACT
CCGGCCCTGCGTCCGCTCAGCCCCGTGGCCCCGCGCACCTACTGCC**ATG**GAGACGCGGCC
TCGTCTCGGGGCCACCTGTTTGCTGGGCTTCAGTTTCCTGCTCCTCGTCATCTCTTCTGA
TGGACATAATGGGCTTGGAAAGGGTTTTGGAGATCATATTCATTGGAGGACACTGGAAGA
TGGGAAGAAAGAAGCAGCTGCCAGTGGACTGCCCCTGATGGTGATTATTCATAAATCCTG
GTGTGGAGCTTGCAAAGCTCTAAAGCCCAAATTTGCAGAATCTACGGAAATTTCAGAACT
CTCCCATAATTTTGTTATGGTAAATCTTGAGGATGAAGAGGAACCCAAAGATGAAGATTT
CAGCCCTGACGGGGGTTATATTCCACGAATCCTTTTTCTGGATCCCAGTGGCAAGGTGCA
TCCTGAAATCATCAATGAGAATGGAAACCCCAGCTACAAGTATTTTTATGTCAGTGCCGA
GCAAGTTGTTCAGGGGATGAAGGAAGCTCAGGAAAGGCTGACGGGTGATGCCTTCAGAAA
GAAACATCTTGAAGATGAATTG**TAA**CATGAATGTGCCCCTTCTTTCATCAGAGTTAGTGT
TCTGGAAGGAAAGCAGCAGGGAAGGGAATATTGAGGAATCATCTAGAACAATTAAGCCGA
CCAGGAAACCTCATTCCTACCTACACTGGAAGGAGCGCTCTCACTGTGGAAGAGTTCTGC
TAACAGAAGCTGGTCTGCATGTTTGTGGATCCAGCGGAGAGTGGCAGACTTTCTTCTCCT
TTTCCCTCTCACCTAAATGTCAACTTGTCATTGAATGTAAAGAATGAAACCTTCTGACAC
AAAA

FIGURE 228

METRPRLGATCLLGFSFLLLVISSDGHNGLGKGFGDHIHWRTLEDGKKEAAASGLPLMVI
IHKSWCGACKALKPKFAESTEISELSHNFVMVNLEDEEEPKDEDFSPDGGYIPRILFLDP
SGKVHPEIINENGNPSYKYFYVSAEQVVQGMKEAQERLTGDAFRKKHLEDEL

Signal peptide:
Amino acids 1-23

Thioredoxin family proteins Homology Block:
Amino acids 58-75

FIGURE 229

CCCACGCGTCCGCCCACGCGTCCGGGTGCCACTCGCGCGCCGGCCGCGCTCCGGGCTTCT
CTTTTCCCTCCGACGCGCCACGGCTGCCCAGACATTCCGGCTGCCGGGTCTGGAGAGCTC
CCCGAACCCCTCCGCGGAGAGGAGCGAGGCGGCGCCAGGGTGGCCCCCGGGGCGCGCTTG
GTCTCGGAGAAGCGGGGACGAGGCCGGAGGATGAGCGACTGAGGGCGACGCGGGCACTGA
CGCGAGTTGGGGCCGCGACTACCGGCAGCTGACAGCGCGATGAGCGACTCCCCAGAGACG
CCCTAGCCCGGTGTGCGCGCCAGGCGGAGCGCGCAGGTGGGGCTGGGCTGTTAGTGGTCC
GCCCCACGCGGGTCGCCGGCCGGCCCAGGATGGGCGCTGGCAACCCGGGCCCGCGCCCGC
CGCTGCTACCCCTGCGCCCGCTGCGAGCCCGGCGTCCGGCCCGCGCCCTGCGCTCATGGA
CGGCGGCTCCCGGCTGGCGGCGGCGCGCCCCCGGGCTGTGAATGCGACTCGCCCCTCGGC
CGCGCTCCCCGCCCGCCCGCCCGCCGGGACGTGGTAGGGG**ATG**CCCAGCTCCACTGCGAT
GGCAGTTGGCGCGCTCTCCAGTTCCCTCCTGGTCACCTGCTGCCTGATGGTGGCTCTGTG
CAGTCCGAGCATCCCGCTGGAGAAGCTGGCCCAGGCACCAGAGCAGCCGGGCCAGGAGAA
GCGTGAGCACGCCACTCGGGACGGCCCGGGGCGGGTGAACGAGCTCGGGCGCCCGGCGAG
GGACGAGGGCGGCAGCGGCCGGGACTGGAAGAGCAAGAGCGGCCGTGGGCTCGCCGGCCG
TGAGCCGTGGAGCAAGCTGAAGCAGGCCTGGGTCTCCCAGGGCGGGGGCGCCAAGGCCGG
GGATCTGCAGGTCCGGCCCCGCGGGGACACCCCGCAGGCGGAAGCCCTGGCCGCAGCCGC
CCAGGACGCGATTGGCCCGGAACTCGCGCCCACGCCCGAGCCACCCGAGGAGTACGTGTA
CCCGGACTACCGTGGCAAGGGCTGCGTGGACGAGAGCGGCTTCGTGTACGCGATCGGGGA
GAAGTTCGCGCCGGGCCCCTCGGCCTGCCCGTGCCTGTGCACCGAGGAGGGGCCGCTGTG
CGCGCAGCCCGAGTGCCCGAGGCTGCACCCGCGCTGCATCCACGTCGACACGAGCCAGTG
CTGCCCGCAGTGCAAGGAGAGGAAGAACTACTGCGAGTTCCGGGGCAAGACCTATCAGAC
TTTGGAGGAGTTCGTGGTGTCTCCATGCGAGAGGTGTCGCTGTGAAGCCAACGGTGAGGT
GCTATGCACAGTGTCAGCGTGTCCCCAGACGGAGTGTGTGGACCCTGTGTACGAGCCTGA
TCAGTGCTGTCCCATCTGCAAAAATGGTCCAAACTGCTTTGCAGAAACCGCGGTGATCCC
TGCTGGCAGAGAAGTGAAGACTGACGAGTGCACCATATGCCACTGTACTTATGAGGAAGG
CACATGGAGAATCGAGCGGCAGGCCATGTGCACGAGACATGAATGCAGGCAAATG**TAG**AC
GCTTCCCAGAACACAAACTCTGACTTTTTCTAGAACATTTTACTGATGTGAACATTCTAG
ATGACTCTGGGAACTATCAGTCAAAGAAGACTTTTGATGAGGAATAATGGAAAATTGTTG
GTACTTTTCCTTTTCTTGATAACAGTTACTACAACAGAAGGAAATGGATATATTTCAAAA
CATCAACAAGAACTTTGGGCATAAAATCCTTCTCTAAATAAATGTGCTATTTTCACAGTA
AGTACACAAAAGTACACTATTATATATCAAATGTATTTCTATAATCCCTCCATTAGAGAG
CTTATATAAGTGTTTTCTATAGATGCAGATTAAAAATGCTGTGTTGTCAACCGTCAAAAA
AAAAAAAAAAAAAAAAAAAAA

FIGURE 230

MPSSTAMAVGALSSSLLVTCCLMVALCSPSIPLEKLAQAPEQPGQEKREHATRDGPGRVN
ELGRPARDEGGSGRDWKSKSGRGLAGREPWSKLKQAWVSQGGGAKAGDLQVRPRGDTPQA
EALAAAAQDAIGPELAPTPEPPEEYVYPDYRGKGCVDESGFVYAIGEKFAPGPSACPCLC
TEEGPLCAQPECPRLHPRCIHVDTSQCCPQCKERKNYCEFRGKTYQTLEEFVVSPCERCR
CEANGEVLCTVSACPQTECVDPVYEPDQCCPICKNGPNCFAETAVIPAGREVKTDECTIC
HCTYEEGTWRIERQAMCTRHECRQM

Important features of the protein:
Signal peptide:
amino acids 1-27

Transmembrane domain:
amino acids 11-30

Glycosaminoglycan attachment site:
amino acids 80-83

N-myristoylation sites:
amino acids 10-15, 102-107, 103-108

Cell attachment sequence:
amino acids 114-117

EGF-like domain cysteine pattern signature:
amino acids 176-187

FIGURE 231

GGCCGGACGCCTCCGCGTTACGGGATGAATTAACGGCGGGTTCCGCACGGAGGTTGTGAC
CCCTACGGAGCCCCAGCTTGCCCACGCACCCCACTCGGCGTCGCGCGGCGTGCCCTGCTT
GTCACAGGTGGGAGGCTGGAACTATCAGGCTGAAAAACAGAGTGGGTACTCTCTTCTGGG
AAGCTGGCAACAAATGGATGATGTGATAT<u>ATG</u>CATTCCAGGGGAAGGGAAATTGTGGTGC
TTCTGAACCCATGGTCAATTAACGAGGCAGTTTCTAGCTACTGCACGTACTTCATAAAGC
AGGACTCTAAAAGCTTTGGAATCATGGTGTCATGGAAAGGGATTTACTTTATACTGACTC
TGTTTTGGGGAAGCTTTTTTGGAAGCATTTTCATGCTGAGTCCCTTTTTACCTTTGATGT
TTGTAAACCCATCTTGGTATCGCTGGATCAACAACCGCCTTGTGGCAACATGGCTCACCC
TACCTGTGGCATTATTGGAGACCATGTTTGGTGTAAAAGTGATTATAACTGGGGATGCAT
TTGTTCCTGGAGAAAGAAGTGTCATTATCATGAACCATCGGACAAGAATGGACTGGATGT
TCCTGTGGAATTGCCTGATGCGATATAGCTACCTCAGATTGGAGAAAATTTGCCTCAAAG
CGAGTCTCAAAGGTGTTCCTGGATTTGGTTGGGCCATGCAGGCTGCTGCCTATATCTTCA
TTCATAGGAAATGGAAGGATGACAAGAGCCATTTCGAAGACATGATTGATTACTTTTGTG
ATATTCACGAACCACTTCAACTCCTCATATTCCCAGAAGGGACTGATCTCACAGAAAACA
GCAAGTCTCGAAGTAATGCATTTGCTGAAAAAAATGGACTTCAGAAATATGAATATGTTT
TACATCCAAGAACTACAGGCTTTACTTTTGTGGTAGACCGTCTAAGAGAAGGTAAGAACC
TTGATGCTGTCCATGATATCACTGTGGCGTATCCTCACAACATTCCTCAATCAGAGAAGC
ACCTCCTCCAAGGAGACTTTCCCAGGGAAATCCACTTTCACGTCCACCGGTATCCAATAG
ACACCCTCCCCACATCCAAGGAGGACCTTCAACTCTGGTGCCACAAACGGTGGGAAGAGA
AAGAAGAGAGGCTGCGTTCCTTCTATCAAGGGGAGAAGAATTTTTATTTTACCGGACAGA
GTGTCATTCCACCTTGCAAGTCTGAACTCAGGGTCCTTGTGGTCAAATTGCTCTCTATAC
TGTATTGGACCCTGTTCAGCCCTGCAATGTGCCTACTCATATATTTGTACAGTCTTGTTA
AGTGGTATTTTATAATCACCATTGTAATCTTTGTGCTGCAAGAGAGAATATTTGGTGGAC
TGGAGATCATAGAACTTGCATGTTACCGACTTTTACACAAACAGCCACATTTAAATTCAA
AGAAAAATGAG<u>TAA</u>GATTATAAGGTTTGCCATGTGAAAACCTAGAGCATATTTTGGAAAT
GTTCTAAACCTTTCTAAGCTCAGATGCATTTTTGCATGACTATGTCGAATATTTCTTACT
GCCATCATTATTTGTTAAAGATATTTTGCACTTAATTTTGTGGAAAAAATATTGCTACAA
TTTTTTTTAATCTCTGAATGTAATTTCGATACTGTGTACATAGCAGGGAGTGATCGGGGT
GAAATAACTTGGGCCAGAATATTATTAAACAATCATCAGGCTTTTAAA

FIGURE 232

MHSRGREIVVLLNPWSINEAVSSYCTYFIKQDSKSFGIMVSWKGIYFILTLFWGSFFGSI
FMLSPFLPLMFVNPSWYRWINNRLVATWLTLPVALLETMFGVKVIITGDAFVPGERSVII
MNHRTRMDWMFLWNCLMRYSYLRLEKICLKASLKGVPGFGWAMQAAAYIFIHRKWKDDKS
HFEDMIDYFCDIHEPLQLLIFPEGTDLTENSKSRSNAFAEKNGLQKYEYVLHPRTTGFTF
VVDRLREGKNLDAVHDITVAYPHNIPQSEKHLLQGDFPREIHFHVHRYPIDTLPTSKEDL
QLWCHKRWEEKEERLRSFYQGEKNFYFTGQSVIPPCKSELRVLVVKLLSILYWTLFSPAM
CLLIYLYSLVKWYFIITIVIFVLQERIFGGLEIIELACYRLLHKQPHLNSKKNE

Important features of the protein:
Signal peptide:
amino acids 1-22

Transmembrane domains:
amino acids 44-63, 90-108, 354-377

FIGURE 233

CGGCTCGAGTGCAGCTGTGGGGAGATTTCAGTGCATTGCCTCCCCTGGGTGCTCTTCATC
TTGGATTTGAAAGTTGAGAGCAGC**ATG**TTTTGCCCACTGAAACTCATCCTGCTGCCAGTG
TTACTGGATTATTCCTTGGGCCTGAATGACTTGAATGTTTCCCCGCCTGAGCTAACAGTC
CATGTGGGTGATTCAGCTCTGATGGGATGTGTTTTCCAGAGCACAGAAGACAAATGTATA
TTCAAGATAGACTGGACTCTGTCACCAGGAGAGCACGCCAAGGACGAATATGTGCTATAC
TATTACTCCAATCTCAGTGTGCCTATTGGGCGCTTCCAGAACCGCGTACACTTGATGGGG
GACATCTTATGCAATGATGGCTCTCTCCTGCTCCAAGATGTGCAAGAGGCTGACCAGGGA
ACCTATATCTGTGAAATCCGCCTCAAAGGGGAGAGCCAGGTGTTCAAGAAGGCGGTGGTA
CTGCATGTGCTTCCAGAGGAGCCCAAAGAGCTCATGGTCCATGTGGGTGGATTGATTCAG
ATGGGATGTGTTTTCCAGAGCACAGAAGTGAAACACGTGACCAAGGTAGAATGGATATTT
TCAGGACGGCGCGCAAAGGAGGAGATTGTATTTCGTTACTACCACAAACTCAGGATGTCT
GTGGAGTACTCCCAGAGCTGGGGCCACTTCCAGAATCGTGTGAACCTGGTGGGGGACATT
TTCCGCAATGACGGTTCCATCATGCTTCAAGGAGTGAGGGAGTCAGATGGAGGAAACTAC
ACCTGCAGTATCCACCTAGGGAACCTGGTGTTCAAGAAAACCATTGTGCTGCATGTCAGC
CCGGAAGAGCCTCGAACACTGGTGACCCCGGCAGCCCTGAGGCCTCTGGTCTTGGGTGGT
AATCAGTTGGTGATCATTGTGGGAATTGTCTGTGCCACAATCCTGCTGCTCCCTGTTCTG
ATATTGATCGTGAAGAAGACCTGTGGAAATAAGAGTTCAGTGAATTCTACAGTCTTGGTG
AAGAACACGAAGAAGACTAATCCAGAGATAAAAGAAAAACCCTGCCATTTTGAAAGATGT
GAAGGGGAGAAACACATTTACTCCCCAATAATTGTACGGGAGGTGATCGAGGAAGAAGAA
CCAAGTGAAAAATCAGAGGCCACCTACATGACCATGCACCCAGTTTGGCCTTCTCTGAGG
TCAGATCGGAACAACTCACTTGAAAAAAAGTCAGGTGGGGGAATGCCAAAAACACAGCAA
GCCTTT**TGA**GAAGAATGGAGAGTCCCTTCATCTCAGCAGCGGTGGAGACTCTCTCCTGTG
TGTGTCCTGGGCCACTCTACCAGTGATTTCAGACTCCCGCTCTCCCAGCTGTCCTCCTGT
CTCATTGTTTGGTCAATACACTGAAGATGGAGAATTTGGAGCCTGGCAGAGAGACTGGAC
AGCTCTGGAGGAACAGGCCTGCTGAGGGGAGGGGAGCATGGACTTGGCCTCTGGAGTGGG
ACACTGGCCCTGGGAACCAGGCTGAGCTGAGTGGCCTCAAACCCCCCGTTGGATCAGACC
CTCCTGTGGGCAGGGTTCTTAGTGGATGAGTTACTGGGAAGAATCAGAGATAAAAACCAA
CCCAAATCAA

FIGURE 234

MFCPLKLILLPVLLDYSLGLNDLNVSPPELTVHVGDSALMGCVFQSTEDKCIFKIDWTLS
PGEHAKDEYVLYYYSNLSVPIGRFQNRVHLMGDILCNDGSLLLQDVQEADQGTYICEIRL
KGESQVFKKAVVLHVLPEEPKELMVHVGGLIQMGCVFQSTEVKHVTKVEWIFSGRRAKEE
IVFRYYHKLRMSVEYSQSWGHFQNRVNLVGDIFRNDGSIMLQGVRESDGGNYTCSIHLGN
LVFKKTIVLHVSPEEPRTLVTPAALRPLVLGGNQLVIIVGIVCATILLLPVLILIVKKTC
GNKSSVNSTVLVKNTKKTNPEIKEKPCHFERCEGEKHIYSPIIVREVIEEEEPSEKSEAT
YMTMHPVWPSLRSDRNNSLEKKSGGGMPKTQQAF

FIGURE 235

TAAAACAGCTACAATATTCCAGGGCCAGTCACTTGCCATTTCTCATAACAGCGTCAGAGA
GAAAGAACTGACTGAAACGTTTGAGATGAAGAAAGTTCTCCTCCTGATCACAGCCATCTT
GGCAGTGGCTGTTGGTTTCCCAGTCTCTCAAGACCAGGAACGAGAAAAAAGAAGTATCAG
TGACAGCGATGAATTAGCTTCAGGGTTTTTGTGTTCCCTTACCCATATCCATTTCGCCC
ACTTCCACCAATTCCATTTCCAAGATTTCCATGGTTTAGACGTAATTTTCCTATTCCAAT
ACCTGAATCTGCCCCTACAACTCCCCTTCCTAGCGAAAAGTAAACAAGAAGGATAAGTCA
CGATAAACCTGGTCACCTGAAATTGAAATTGAGCCACTTCCTTGAAGAATCAAAATTCCT
GTTAATAAAAGAAAAACAAATGTAATTGAAATAGCACACAGCATTCTCTAGTCAATATCT
TTAGTGATCTTCTTTAATAAACATGAAAGCAAAGATTTTGGTTTCTTAATTTCCACA

FIGURE 236

MKKVLLLITAILAVAVGFPVSQDQEREKRSISDSDELASGFFVFPYPYPFRPLPPIPFPR
FPWFRRNFPIPIPESAPTTPLPSEK

Important features of the protein:
Signal peptide:
amino acids 1-17

Homologous region to B3-hordein:
amino acids 47-85

FIGURE 237

TCGCC**<u>ATG</u>**GCCTCTGCCGGAATGCAGATCCTGGGAGTCGTCCTGACACTGCTGGGCTGGG
TGAATGGCCTGGTCTCCTGTGCCCTGCCCATGTGGAAGGTGACCGCTTTCATCGGCAACA
GCATCGTGGTGGCCCAGGTGGTGTGGGAGGGCCTGTGGATGTCCTGCGTGGTGCAGAGCA
CCGGCCAGATGCAGTGCAAGGTGTACGACTCACTGCTGGCGCTGCCACAGGACCTGCAGG
CTGCACGTGCCCTCTGTGTCATCGCCCTCCTTGTGGCCCTGTTCGGCTTGCTGGTCTACC
TTGCTGGGGCCAAGTGTACCACCTGTGTGGAGGAGAAGGATTCCAAGGCCCGCCTGGTGC
TCACCTCTGGGATTGTCTTTGTCATCTCAGGGGTCCTGACGCTAATCCCCGTGTGCTGGA
CGGCGCATGCCATCATCCGGGACTTCTATAACCCCCTGGTGGCTGAGGCCCAAAAGCGGG
AGCTGGGGGCCTCCCTCTACTTGGGCTGGGCGGCCTCAGGCCTTTTGTTGCTGGGTGGGG
GGTTGCTGTGCTGCACTTGCCCCTCGGGGGGGTCCCAGGGCCCCAGCCATTACATGGCCC
GCTACTCAACATCTGCCCCTGCCATCTCTCGGGGGCCCTCTGAGTACCCTACCAAGAATT
ACGTC**<u>TGA</u>**CGTGGAGGGGAATGGGGGCTCCGCTGGCGCTAGAGCCATCCAGAAGTGGCAG
TGCCCAACAGCTTTGGGATGGGTTCGTACCTTTTGTTTCTGCCTCCTGCTATTTTTCTTT
TGACTGAGGATATTTAAAATTCATTTGAAAACTGAGCCAAGGTGTTGACTCAGACTCTCA
CTTAGGCTCTGCTGTTTCTCACCCTTGGATGATGGAGCCAAAGAGGGGATGCTTTGAGAT
TCTGGATCTTGACATGCCCATCTTAGAAGCCAGTCAAGCTATGGAACTAATGCGGAGGCT
GCTTGCTGTGCTGGCTTTGCAACAAGACAGACTGTCCCCAAGAGTTCCTGCTGCTGCTGG
GGGCTGGGCTTCCCTAGATGTCACTGGACAGCTGCCCCCCATCCTACTCAGGTCTCTGGA
GCTCCTCTCTTCACCCCTGGAAAAACAAATCATCTGTTAACAAAGGACTGCCCACCTCCG
GAACTTCTGACCTCTGTTTCCTCCGTCCTGATAAGACGTCCACCCCCCAGGGCCAGGTCC
CAGCTATGTAGACCCCCGCCCCCACCTCCAACACTGCACCCTTCTGCCCTGCCCCCCTCG
TCTCACCCCCTTTACACTCACATTTTTATCAAATAAAGCATGTTTTGTTAGTGCA

FIGURE 238

MASAGMQILGVVLTLLGWVNGLVSCALPMWKVTAFIGNSIVVAQVVWEGLWMSCVVQSTG
QMQCKVYDSLLALPQDLQAARALCVIALLVALFGLLVYLAGAKCTTCVEEKDSKARLVLT
SGIVFVISGVLTLIPVCWTAHAIIRDFYNPLVAEAQKRELGASLYLGWAASGLLLLGGGL
LCCTCPSGGSQGPSHYMARYSTSAPAISRGPSEYPTKNYV

Transmembrane domains:
amino acids 8-30 (type II), 82-102, 121-140, 166-186

FIGURE 239

AGTGACAATCTCAGAGCAGCTTCTACACCACAGCCATTTCCAGC**ATG**AAGATCACTGGGG
GTCTCCTTCTGCTCTGTACAGTGGTCTATTTCTGTAGCAGCTCAGAAGCTGCTAGTCTGT
CTCCAAAAAAAGTGGACTGCAGCATTTACAAGAAGTATCCAGTGGTGGCCATCCCCTGCC
CCATCACATACCTACCAGTTTGTGGTTCTGACTACATCACCTATGGGAATGAATGTCACT
TGTGTACCGAGAGCTTGAAAAGTAATGGAAGAGTTCAGTTTCTTCACGATGGAAGTTGC**T**
AAATTCTCCATGGACATAGAGAGAAAGGAATGATATTCTCATCATCATCTTCATCATCCC
AGGCTCTGACTGAGTTTCTTTCAGTTTTACTGATGTTCTGGGTGGGGGACAGAGCCAGAT
TCAGAGTAATCTTGACTGAATGGAGAAAGTTTCTGTGCTACCCCTACAAACCCATGCCTC
ACTGACAGACCAGCATTTTTTTTTAACACGTCAATAAAAAAATAATCTCCCAGA

FIGURE 240

MKITGGLLLLCTVVYFCSSSEAASLSPKKVDCSIYKKYPVVAIPCPITYLPVCGSDYITY
GNECHLCTESLKSNGRVQFLHDGSC

Signal peptide:
amino acids 1-19

FIGURE 241

CCCGCGCCCGGTTCTCCCTCGCAGCACCTCGAAGTGCGCCCCTCGCCCTCCTGCTCGCGC
CCCGCCGCC**ATG**GCTGCCTCCCCCGCGCGGCCTGCTGTCCTGGCCCTGACCGGGCTGGCG
CTGCTCCTGCTCCTGTGCTGGGGCCCAGGTGGCATAAGTGGAAATAAACTCAAGCTGATG
CTTCAAAAACGAGAAGCACCTGTTCCAACTAAGACTAAAGTGGCCGTTGATGAGAATAAA
GCCAAAGAATTCCTTGGCAGCCTGAAGCGCCAGAAGCGGCAGCTGTGGGACCGGACTCGG
CCCGAGGTGCAGCAGTGGTACCAGCAGTTTCTCTACATGGGCTTTGATGAAGCGAAATTT
GAAGATGACATCACCTATTGGCTTAACAGAGATCGAAATGGACATGAATACTATGGCGAT
TACTACCAACGTCACTATGATGAAGACTCTGCAATTGGTCCCCGGAGCCCCTACGGCTTT
AGGCATGGAGCCAGCGTCAACTACGATGACTAC**TAA**CCATGACTTGCCACACGCTGTACA
AGAAGCAAATAGCGATTCTCTTCATGTATCTCCTAATGCCTTACACTACTTGGTTTCTGA
TTTGCTCTATTTCAGCAGATCTTTTCTACCTACTTTGTGTGATCAAAAAAGAAGAGTTAA
AACAACACATGTAAATGCCTTTTGATATTTCATGGAATGCCTCTCATTTAAAAATAGAA
ATAAAGCATTTTGTTAAAAAGA

FIGURE 242

MAASPARPAVLALTGLALLLLLCWGPGGISGNKLKLMLQKREAPVPTKTKVAVDENKAKE
FLGSLKRQKRQLWDRTRPEVQQWYQQFLYMGFDEAKFEDDITYWLNRDRNGHEYYGDYYQ
RHYDEDSAIGPRSPYGFRHGASVNYDDY

Signal peptide:
amino acids 1-30

FIGURE 243

CTCCATTAAACCACCACCAGCTCCCCAAGCCACCCCTTCAGCC**ATG**AAGTTCCTGCTCCT
GGTCTTGGCAGCCCTCGGATTCCTGACCCAGGTGATCCCAGCCAGTGCAGGTGGGTCAAA
ATGTGTGAGTAACACCCCAGGATACTGCAGGACATGTTGCCACTGGGGGGAGACAGCATT
GTTCATGTGCAACGCTTCCAGAAAATGCTGCATCAGCTACTCCTTCCTGCCGAAGCCTGA
CCTACCACAGCTCATCGGTAACCACTGGCAATCAAGGAGAAGAAACACACAAAGGAAAGA
CAAGAAGCAACAAACGACCGTAACATCA**TAA**TAACCACTGCTATCGCCTCCACCAACTCA
GAGAAATATCATTTCCACAGTTCCAATTCCTCCTACATTGCTGAGTACTAGCCAAGGCTC
CTCTTTATGGGGCAGATATCTATAGCCAACCCCAAAACTTCTGTCTTCTATCATTCTGTC
ATTCATCTAGTAACTAATTTGGAGTTTGTATCTATCTTACGAGAACAATCATCATGCAGA
TTCGTCCACAGGGGATCTGTCAGTTTGGGTCCTCCAAATGAAAAATGTCAAGACAGAATT
GGACATGCAAAAGATTGACTGGGAGAACACACCTCTGATGGACAAAGGTGAGACAGAGCA
GCCACAGGCAGGGAGAGCCTTCAGACTGCAACGCTGGCCTGATACGTGTCAAAGGAGAGA
GGGATAGAGGAGGATTGAATAGAAGGAGACTAAGACTGCAGCTCTAAGAAAGTCTCAGCC
AAACAGATGGGGAGGCCCAAAGCAAGGCTTGCCCCTCAGAGGAGCTCACGCAGGGCAGGA
ATAGCCAGGTTCTCATATCCCAGGGGTTCAGACTTGGCTGAGAACAGCCCCTGGAGAACA
TGGGGTGACTGCTACCATAGGTCTGGAAGTATGAGGCTGTCCACCAACTATCCCCTTGAA
GCAAGTTCTCTTGAAAGGAAATCTAAACAGTGCACCCCCATGGCTGCCACGGAGTATAAG
GAGGGAGAGAAAGGAGCTGAAAGTCTAGGTTTGGCCAGCTAGGTAGACTGACTTGTGAGG
TATTTATTTATTCATTTGAGTAACAAAGCAGACAGAATACATAGCCACCATTGGTAGTAC
ACCCCAAAAGCAAGGATGGCATGATGCTGGTGACTCAAACGTGCCTACTCATGGTGTCAA
ATTGGCATAATCCTCTTGGGAAGCTGTGTGGAAATAAGCACAGAGAAGCAGAACTCTAAT
TGCTTAATCCACTAAACATTACTTCTGGGAATTGGCTCATCATAAATTATCCAAGAGAAA
GCACAAAGTTATGGGCACAAAGGTTTTCCATATAATATTATTTAAAATGCTGAGAAAATG
AAAAAATCTAAATGGTGAAATATATACTAATGCCATCTATAAATACAAACAAATAGAATG
TTTATAGAATAATGGAACATAATAACATTATTCAAAATTGCATTTATGCTATAGTTGTCA
AAATTGTCTCCTTATATGATACAAAACTCATGAAAATTATGACTTTTTTGTTTGGTTGGA
AAGCAGAATTATGCATAAATTTCCTCTTACAGTTCGATGCCCATTAGTTTTATATAACAT
TTATTTGACACGTACTGACTTCTATCTGAGAAGAACAAACCAAAACACTCAGGCCTAAAT
AATTAAAAACGGTCCTAAAAACTAGCAAACCAGATAAGAAAAGATGTTAATGCCCATTCC
CTAACTTATGTCTTAGACCAAAATTAATTCTAGATGGTTTTAAAATGACAGTGTAAAAGT
AAAGTATTAAAAGATTGTGTGGTCAAATATTCAATTTAAGAGCAAGGAAATTCTTATAAA
TATAACAATAGAGGCAGAACTCATGTAAGAATAAATTGATTAGGTGGTATTAAATATTAA
GTTCTTATGTATGTCAAAAGATATCATTTTGAAATTCATCCATCTTATTGGGTATTGCAG
GAGTTCATTCCTTTTTGTTTATAAATACTCTTCCGTCATATGAATAGTATTCATTTGTAT
ACTGGTTTGTTGATGGACATTTGGGTTGTTCCCAGTTTATGGCTATTACAAATAAAGCTT
CTATGAACATTTATGTACA

FIGURE 244

MKFLLLVLAALGFLTQVIPASAGGSKCVSNTPGYCRTCCHWGETALFMCNASRKCCISYS
FLPKPDLPQLIGNHWQSRRRNTQRKDKKQQTTVTS

Important features of the protein:
Signal peptide:
amino acids 1-16

Transmembrane domain:
amino acids 1-22

N-glycosylation site:
amino acids 50-53

cAMP- and cGMP-dependent protein kinase phosphorylation site:
amino acids 79-82

N-myristoylation site:
amino acids 23-28

FIGURE 245

GGAGAGAGGCGCGCGGGTGAAAGGCGCATTGATGCAGCCTGCGGCGGCCTCGGAGCGCGG
CGGAGCCAGACGCTGACCACGTTCCTCTCCTCGGTCTCCTCCGCCTCCAGCTCCGCGCTG
CCCGGCAGCCGGGAGCC<u>ATG</u>CGACCCCAGGGCCCCGCCGCCTCCCCGCAGCGGCTCCGCG
GCCTCCTGCTGCTCCTGCTGCTGCAGCTGCCCGCGCCGTCGAGCGCCTCTGAGATCCCCA
AGGGGAAGCAAAAGGCGCAGCTCCGGCAGAGGGAGGTGGTGGACCTGTATAATGGAATGT
GCTTACAAGGGCCAGCAGGAGTGCCTGGTCGAGACGGGAGCCCTGGGGCCAATGTTATTC
CGGGTACACCTGGGATCCCAGGTCGGGATGGATTCAAAGGAGAAAAGGGGGAATGTCTGA
GGGAAAGCTTTGAGGAGTCCTGGACACCCAACTACAAGCAGTGTTCATGGAGTTCATTGA
ATTATGGCATAGATCTTGGGAAAATTGCGGAGTGTACATTTACAAAGATGCGTTCAAATA
GTGCTCTAAGAGTTTTGTTCAGTGGCTCACTTCGGCTAAAATGCAGAAATGCATGCTGTC
AGCGTTGGTATTTCACATTCAATGGAGCTGAATGTTCAGGACCTCTTCCCATTGAAGCTA
TAATTTATTTGGACCAAGGAAGCCCTGAAATGAATTCAACAATTAATATTCATCGCACTT
CTTCTGTGGAAGGACTTTGTGAAGGAATTGGTGCTGGATTAGTGGATGTTGCTATCTGGG
TTGGCACTTGTTCAGATTACCCAAAAGGAGATGCTTCTACTGGATGGAATTCAGTTTCTC
GCATCATTATTGAAGAACTACCAAAA<u>TAA</u>ATGCTTTAATTTTCATTTGCTACCTCTTTTT
TTATTATGCCTTGGAATGGTTCACTTAAATGACATTTTAAATAAGTTTATGTATACATCT
GAATGAAAAGCAAAGCTAAATATGTTTACAGACCAAAGTGTGATTTCACACTGTTTTTAA
ATCTAGCATTATTCATTTTGCTTCAATCAAAAGTGGTTTCAATATTTTTTTTAGTTGGTT
AGAATACTTTCTTCATAGTCACATTCTCTCAACCTATAATTTGGAATATTGTTGTGGTCT
TTTGTTTTTTCTCTTAGTATAGCATTTTTAAAAAAATATAAAAGCTACCAATCTTTGTAC
AATTTGTAAATGTTAAGAATTTTTTTATATCTGTTAAATAAAAATTATTTCCAACA

FIGURE 246

MRPQGPAASPQRLRGLLLLLLLQLPAPSSASEIPKGKQKAQLRQREVVDLYNGMCLQGPA
GVPGRDGSPGANVIPGTPGIPGRDGFKGEKGECLRESFEESWTPNYKQCSWSSLNYGIDL
GKIAECTFTKMRSNSALRVLFSGSLRLKCRNACCQRWYFTFNGAECSGPLPIEAIIYLDQ
GSPEMNSTINIHRTSSVEGLCEGIGAGLVDVAIWVGTCSDYPKGDASTGWNSVSRIIIEE
LPK

Signal peptide:
amino acids 1-30

Transmembrane domain:
amino acids 195-217

FIGURE 247

GGCCGTTGGTTGGTGCGCGGCTGAAGGGTGTGGCGCGAGCAGCGTCGTTGGTTGGCCGGC
GGCGGGCCGGGACGGGC**<u>ATG</u>**GCCCTGCTGCTGTGCCTGGTGTGCCTGACGGCGGCGCTGG
CCCACGGCTGTCTGCACTGCCACAGCAACTTCTCCAAGAAGTTCTCCTTCTACCGCCACC
ATGTGAACTTCAAGTCCTGGTGGGTGGGCGACATCCCCGTGTCAGGGGCGCTGCTCACCG
ACTGGAGCGACGACACGATGAAGGAGCTGCACCTGGCCATCCCCGCCAAGATCACCCGGG
AGAAGCTGGACCAAGTGGCGACAGCAGTGTACCAGATGATGGATCAGCTGTACCAGGGGA
AGATGTACTTCCCCGGGTATTTCCCCAACGAGCTGCGAAACATCTTCCGGGAGCAGGTGC
ACCTCATCCAGAACGCCATCATCGAAAGGCACCTGGCACCAGGCAGCTGGGGAGGAGGGC
AGCTCTCCAGGGAGGGACCCAGCCTAGCACCTGAAGGATCAATGCCATCACCCCGCGGGG
ACCTCCCC**<u>TAA</u>**GTAGCCCCCAGAGGCGCTGGGAGTGTTGCCACCGCCCTCCCCTGAAGTT
TGCTCCATCTCACGCTGGGGGTCAACCTGGGGACCCCTTCCCTCCGGGCCATGGACACAC
ATACATGAAAACCAGGCCGCATCGACTGTCAGCACCGCTGTGGCATCTTCCAGTACGAGA
CCATCTCCTGCAACAACTGCACAGACTCGCACGTCGCCTGCTTTGGCTATAACTGCGAGT
AGGGCTCAGGCATCACACCCACCCGTGCCAGGGCCCTACTGTCCCTGGGGTCCCAGGCTC
TCCTTGGAGGGGGCTCCCCGCCTTCCACCTGGCTGTCATCGGGTAGGGCGGGGCCGTGGG
TTCAGGGGCGCACCACTTCCAAGCCTGTGTCCCACAGGTCCTCGGCGCAGTGGAAGTCAG
CTGTCCAGGGCCTCCTGAACTACATAAATAACTGGCACAAGTAAGTCCCCTCCTCAAACC
AACACAGGCAGTGTGTGTATGTGAGCACCTCGTGGGTGAGTATGTGTGGGGCACAGGCTG
GCTCCCTCAGCTCCCACGTCCTAGAGGGGCTCCCGAGGAGGTGGAACCTCAACCCAGCTC
TGCGCAGGAGGCGGCTGCAGTCCTTTTCTCCCTCAAAGGTCTCCGACCCTCAGCTGGAGG
CGGGCATCTTTCCTAAAGGGTCCCCATAGGGTCTGGTTCCACCCCATCCCAGGTCTGTGG
TCAGAGCCTGGGAGGGTTCCCTACGATGGTTAGGGGTGCCCCATGGAGGGGCTGACTGCC
CCACATTGCCTTTCAGACAGGACACGAGCATGAGGTAAGGCCGCCCTGACCTGGACTTCA
GGGGGAGGGGGTAAAGGGAGAGAGGAGGGGGGCTAGGGGGTCCTCTAGATCAGTGGGGGC
ACTGCAGGTGGGGCTCTCCCTATACCTGGGACACCTGCTGGATGTCACCTCTGCAACCAC
ACCCATGTGGTGGTTTCATGAACAGACCACGCTCCTCTGCCTTCTCCTGGCCTGGGACAC
ACAGAGCCACCCCGGCCTTGTGAGTGACCCAGAGAAGGGAGGCCTCGGGAGAAGGGGTGC
TCGTAAGCCAACACCAGCGTGCCGCGGCCTGCACACCCTTCGGACATCCCAGGCACGAGG
GTGTCGTGGATGTGGCCACACATAGGACCACACGTCCCAGCTGGGAGGAGAGGCCTGGGG
CCCCCAGGGAGGGAGGCAGGGGGTGGGGACATGGAGAGCTGAGGCAGCCTCGTCTCCCC
GCAGCCTGGTATCGCCAGCCTTAAGGTGTCTGGAGCCCCCACACTTGGCCAACCTGACCT
TGGAAGATGCTGCTGAGTGTCTCAAGCAGCACTGACAGCAGCTGGGCCTGCCCCAGGGCA
ACGTGGGGGCGGAGACTCAGCTGGACAGCCCCTGCCTGTCACTCTGGAGCTGGGCTGCTG
CTGCCTCAGGACCCCCTCTCCGACCCCGGACAGAGCTGAGCTGGCCAGGGCCAGGAGGGC
GGGAGGGAGGGAATGGGGGTGGGCTGTGCGCAGCATCAGCGCCTGGGCAGGTCCGCAGAG
CTGCGGGATGTGATTAAAGTCCCTGATGTTTCTC

FIGURE 248

MALLLCLVCLTAALAHGCLHCHSNFSKKFSFYRHHVNFKSWWVGDIPVSGALLTDWSDDT
MKELHLAIPAKITREKLDQVATAVYQMMDQLYQGKMYFPGYFPNELRNIFREQVHLIQNA
IIERHLAPGSWGGGQLSREGPSLAPEGSMPSPRGDLP

Signal peptide:
amino acids 1-15

FIGURE 249

CGACG**ATG**CTACGCGCGCCCGGCTGCCTCCTCCGGACCTCCGTAGCGCCTGCCGCGGCCC
TGGCTGCGGCGCTGCTCTCGTCGCTTGCGCGCTGCTCTCTTCTAGAGCCGAGGGACCCGG
TGGCCTCGTCGCTCAGCCCCTATTTCGGCACCAAGACTCGCTACGAGGATGTCAACCCCG
TGCTATTGTCGGGCCCCGAGGCTCCGTGGCGGGACCCTGAGCTGCTGGAGGGGACCTGCA
CCCCGGTGCAGCTGGTCGCCCTCATTCGCCACGGCACCCGCTACCCCACGGTCAAACAGA
TCCGCAAGCTGAGGCAGCTGCACGGGTTGCTGCAGGCCCGCGGGTCCAGGGATGGCGGGG
CTAGTAGTACCGGCAGCCGCGACCTGGGTGCAGCGCTGGCCGACTGGCCTTTGTGGTACG
CGGACTGGATGGACGGGCAGCTAGTAGAGAAGGGACGGCAGGATATGCGACAGCTGGCGC
TGCGTCTGGCCTCGCTCTTCCCGGCCCTTTTCAGCCGTGAGAACTACGGCCGCCTGCGGC
TCATCACCAGTTCCAAGCACCGCTGCATGGATAGCAGCGCCGCCTTCCTGCAGGGGCTGT
GGCAGCACTACCACCCTGGCTTGCCGCCGCCGGACGTCGCAGATATGGAGTTTGGACCTC
CAACAGTTAATGATAAACTAATGAGATTTTTGATCACTGTGAGAAGTTTTAACTGAAG
TAGAAAAAAATGCTACAGCTCTTTATCACGTGGAAGCCTTCAAAACTGGACCAGAAATGC
AGAACATTTTAAAAAAAGTTGCAGCTACTTTGCAAGTGCCAGTAAATGATTTAAATGCAG
ATTTAATTCAAGTAGCCTTTTTCACCTGTTCATTTGACCTGGCAATTAAAGGTGTTAAAT
CTCCTTGGTGTGATGTTTTTGACATAGATGATGCAAAGGTATTAGAATATTTAAATGATC
TGAAACAATATTGGAAAAGAGGATATGGGTATACTATTAACAGTCGATCCAGCTGCACCT
TGTTTCAGGATATCTTTCAGCACTTGGACAAAGCAGTTGAACAGAAACAAAGGTCTCAGC
CAATTTCTTCTCCAGTCATCCTCCAGTTTGGTCATGCAGAGACTCTTCTTCCACTGCTTT
CTCTCATGGGCTACTTCAAAGACAAGGAACCCCTAACAGCGTACAATTACAAAAAACAAA
TGCATCGGAAGTTCCGAAGTGGTCTCATTGTACCTTATGCCTCGAACCTGATATTTGTGC
TTTACCACTGTGAAAATGCTAAGACTCCTAAAGAACAATTCCGAGTGCAGATGTTATTAA
ATGAAAAGGTGTTACCTTTGGCTTACTCACAAGAAACTGTTTCATTTTATGAAGATCTGA
AGAACCACTACAAGGACATCCTTCAGAGTTGTCAAACCAGTGAAGAATGTGAATTAGCAA
GGGCTAACAGTACATCTGATGAACTA**TGA**GTAACTGAAGAACATTTTTAATTCTTTAGGA
ATCTGCAATGAGTGATTACATGCTTGTAATAGGTAGGCAATTCCTTGATTACAGGAAGCT
TTTATATTACTTGAGTATTTCTGTCTTTTCACAGAAAAACATTGGGTTTCTCTCTGGGTT
TGGACATGAAATGTAAGAAAAGATTTTTCACTGGAGCAGCTCTCTTAAGGAGAAACAAAT
CTATTTAGAGAAACAGCTGGCCCTGCAAATGTTTACAGAAATGAAATTCTTCCTACTTAT
ATAAGAAATCTCACACTGAGATAGAATTGTGATTTCATAATAACACTTGAAAAGTGCTGG
AGTAACAAAATATCTCAGTTGGACCATCCTTAACTTGATTGAACTGTCTAGGAACTTTAC
AGATTGTTCTGCAGTTCTCTCTTCTTTTCCTCAGGTAGGACAGCTCTAGCATTTTCTTAA
TCAGGAATATTGTGGTAAGCTGGGAGTATCACTCTGGAAGAAAGTAACATCTCCAGATGA
GAATTTGAAACAAGAAACAGAGTGTTGTAAAAGGACACCTTCACTGAAGCAAGTCGGAAA
GTACAATGAAAATAAATATTTTTGGTATTTATTTATGAAATATTTGAACATTTTTTCAAT
AATTCCTTTTTACTTCTAGGAAGTCTCAAAAGACCATCTTAAATTATTATATGTTTGGAC
AATTAGCAACAAGTCAGATAGTTAGAATCGAAGTTTTTCAAATCCATTGCTTAGCTAACT
TTTTCATTCTGTCACTTGGCTTCGATTTTTATATTTCCTATTATATGAAATGTATCTTT
TGGTTGTTTGATTTTTCTTTCTTTCTTTGTAAATAGTTCTGAGTTCTGTCAAATGCCGTG
AAAGTATTTGCTATAATAAAGAAAATTCTTGTGACTTTAAAAAAAAA

FIGURE 250

MLRAPGCLLRTSVAPAAALAAALLSSLARCSLLEPRDPVASSLSPYFGTKTRYEDVNPVL
LSGPEAPWRDPELLEGTCTPVQLVALIRHGTRYPTVKQIRKLRQLHGLLQARGSRDGGAS
STGSRDLGAALADWPLWYADWMDGQLVEKGRQDMRQLALRLASLFPALFSRENYGRLRLI
TSSKHRCMDSSAAFLQGLWQHYHPGLPPPDVADMEFGPPTVNDKLMRFFDHCEKFLTEVE
KNATALYHVEAFKTGPEMQNILKKVAATLQVPVNDLNADLIQVAFFTCSFDLAIKGVKSP
WCDVFDIDDAKVLEYLNDLKQYWKRGYGYTINSRSSCTLFQDIFQHLDKAVEQKQRSQPI
SSPVILQFGHAETLLPLLSLMGYFKDKEPLTAYNYKKQMHRKFRSGLIVPYASNLIFVLY
HCENAKTPKEQFRVQMLLNEKVLPLAYSQETVSFYEDLKNHYKDILQSCQTSEECELARA
NSTSDEL

Important features:
Signal sequence
amino acids 1-30

N-glycosylation sites:
amino acids 242-246, 481-485

N-myristoylation sites.
amino acids 107-113, 113-119, 117-123, 118-124, 128-134

Endoplasmic reticulum targeting sequence:
amino acids 484-489

FIGURE 251

GGAGAGCCGCGGCTGGGACCGGAGTGGGGAGCGCGGCGTGGAGGTGCCACCCGGCGCGGG
TGGCGGAGAGATCAGAAGCCTCTTCCCCAAGCCGAGCCAACCTCAGCGGGGACCCGGGCT
CAGGGACGCGGCGGCGGCGGCGGCGACTGCAGTGGCTGGACG**ATG**GCAGCGTCCGCCGGA
GCCGGGGCGGTGATTGCAGCCCCAGACAGCCGGCGCTGGCTGTGGTCGGTGCTGGCGGCG
GCGCTTGGGCTCTTGACAGCTGGAGTATCAGCCTTGGAAGTATATACGCCAAAAGAAATC
TTCGTGGCAAATGGTACACAAGGGAAGCTGACCTGCAAGTTCAAGTCTACTAGTACGACT
GGCGGGTTGACCTCAGTCTCCTGGAGCTTCCAGCCAGAGGGGGCCGACACTACTGTGTCG
TTTTTCCACTACTCCCAAGGGCAAGTGTACCTTGGGAATTATCCACCATTTAAAGACAGA
ATCAGCTGGGCTGGAGACCTTGACAAGAAAGATGCATCAATCAACATAGAAAATATGCAG
TTTATACACAATGGCACCTATATCTGTGATGTCAAAAACCCTCCTGACATCGTTGTCCAG
CCTGGACACATTAGGCTCTATGTCGTAGAAAAAGAGAATTTGCCTGTGTTTCCAGTTTGG
GTAGTGGTGGGCATAGTTACTGCTGTGGTCCTAGGTCTCACTCTGCTCATCAGCATGATT
CTGGCTGTCCTCTATAGAAGGAAAAACTCTAAACGGGATTACACTGGCTGCAGTACATCA
GAGAGTTTGTCACCAGTTAAGCAGGCTCCTCGGAAGTCCCCCTCCGACACTGAGGGTCTT
GTAAAGAGTCTGCCTTCTGGATCTCACCAGGGCCCAGTCATATATGCACAGTTAGACCAC
TCCGGCGGACATCACAGTGACAAGATTAACAAGTCAGAGTCTGTGGTGTATGCGGATATC
CGAAAGAAT**TAA**GAGAATACCTAGAACATATCCTCAGCAAGAAACAAAACCAAACTGGAC
TCTCGTGCAGAAAATGTAGCCCATTACCACATGTAGCCTTGGAGACCCAGGCAAGGACAA
GTACACGTGTACTCACAGAGGGAGAGAAAGATGTGTACAAAGGATATGTATAAATATTCT
ATTTAGTCATCCTGATATGAGGAGCCAGTGTTGCATGATGAAAAGATGGTATGATTCTAC
ATATGTACCCATTGTCTTGCTGTTTTTGTACTTTCTTTTCAGGTCATTTACAATTGGGAG
ATTTCAGAAACATTCCTTTCACCATCATTTAGAAATGGTTTGCCTTAATGGAGACAATAG
CAGATCCTGTAGTATTTCCAGTAGACATGGCCTTTTAATCTAAGGGCTTAAGACTGATTA
GTCTTAGCATTTACTGTAGTTGGAGGATGGAGATGCTATGATGGAAGCATACCCAGGGTG
GCCTTTAGCACAGTATCAGTACCATTTATTTGTCTGCCGCTTTTAAAAAATACCCATTGG
CTATGCCACTTGAAAACAATTTGAGAAGTTTTTTTGAAGTTTTTCTCACTAAAATATGGG
GCAATTGTTAGCCTTACATGTTGTGTAGACTTACTTTAAGTTTGCACCCTTGAAATGTGT
CATATCAATTTCTGGATTCATAATAGCAAGATTAGCAAAGGATAAATGCCGAAGGTCACT
TCATTCTGGACACAGTTGGATCAATACTGATTAAGTAGAAAATCCAAGCTTTGCTTGAGA
ACTTTTGTAACGTGGAGAGTAAAAAGTATCGGTTTTA

FIGURE 252

MAASAGAGAVIAAPDSRRWLWSVLAAALGLLTAGVSALEVYTPKEIFVANGTQGKLTCKF
KSTSTTGGLTSVSWSFQPEGADTTVSFFHYSQGQVYLGNYPPFKDRISWAGDLDKKDASI
NIENMQFIHNGTYICDVKNPPDIVVQPGHIRLYVVEKENLPVFPVWVVVGIVTAVVLGLT
LLISMILAVLYRRKNSKRDYTGCSTSESLSPVKQAPRKSPSDTEGLVKSLPSGSHQGPVI
YAQLDHSGGHHSDKINKSESVVYADIRKN

Signal peptide:
amino acids 1-37

Transmembrane domain:
amino acids 161-183

FIGURE 253

GTGACACTATAGAAGAGCTATGACGTCGCATGCACGCGTACGTAAGCTCGGAATTCGGCT
CGAGGCTGGTGGGAAGAAGCCGAG<u>ATG</u>GCGGCAGCCAGCGCTGGGGCAACCCGGCTGCTC
CTGCTCTTGCTGATGGCGGTAGCAGCGCCCAGTCGAGCCCGGGGCAGCGGCTGCCGGGCC
GGGACTGGTGCGCGAGGGGCTGGGGCGGAAGGTCGAGAGGGCGAGGCCTGTGGCACGGTG
GGGCTGCTGCTGGAGCACTCATTTGAGATCGATGACAGTGCCAACTTCCGGAAGCGGGGC
TCACTGCTCTGGAACCAGCAGGATGGTACCTTGTCCCTGTCACAGCGGCAGCTCAGCGAG
GAGGAGCGGGGCCGACTCCGGGATGTGGCAGCCCTGAATGGCCTGTACCGGGTCCGGATC
CCAAGGCGACCCGGGGCCCTGGATGGCCTGGAAGCTGGTGGCTATGTCTCCTCCTTTGTC
CCTGCGTGCTCCCTGGTGGAGTCGCACCTGTCGGACCAGCTGACCCTGCACGTGGATGTG
GCCGGCAACGTGGTGGGCGTGTCGGTGGTGACGCACCCCGGGGGCTGCCGGGGCCATGAG
GTGGAGGACGTGGACCTGGAGCTGTTCAACACCTCGGTGCAGCTGCAGCCGCCCACCACA
GCCCCAGGCCCTGAGACGGCGGCCTTCATTGAGCGCCTGGAGATGGAACAGGCCCAGAAG
GCCAAGAACCCCCAGGAGCAGAAGTCCTTCTTCGCCAAATACTGGATGTACATCATTCCC
GTCGTCCTGTTCCTCATGATGTCAGGAGCGCCAGACACCGGGGGCCAGGGTGGGGGTGGG
GGTGGGGGTGGTGGTGGGGGTAGTGGCCTTTGCTGTGTGCCACCCTCCCTG<u>TAA</u>GTCTAT
TTAAAAACATCGACGATACATTGAAATGTGTGAACGTTTTGAAAAGCTACAGCTTCCAGC
AGCCAAAAGCAACTGTTGTTTTGGCAAGACGGTCCTGATGTACAAGCTTGATTGAAATTC
ACTGCTCACTTGATACGTTATTCAGAAACCCAAGGAATGGCTGTCCCCATCCTCATGTGG
CTGTGTGGAGCTCAGCTGTGTTGTGTGGCAGTTTATTAAACTGTCCCCCAGATCGACACG
CAAAAAAAAA

FIGURE 254

MAAASAGATRLLLLLLMAVAAPSRARGSGCRAGTGARGAGAEGREGEACGTVGLLLEHSF
EIDDSANFRKRGSLLWNQQDGTLSLSQRQLSEEERGRLRDVAALNGLYRVRIPRRPGALD
GLEAGGYVSSFVPACSLVESHLSDQLTLHVDVAGNVVGVSVVTHPGGCRGHEVEDVDLEL
FNTSVQLQPPTTAPGPETAAFIERLEMEQAQKAKNPQEQKSFFAKYWMYIIPVVLFLMMS
GAPDTGGQGGGGGGGGGGGSGLCCVPPSL

Signal peptide:
amino acids 1-24

Transmembrane domain:
amino acids 226-243

FIGURE 255

GCGACGCGCGGCGGGGCGGCGAGAGGAAACGCGGCGCCGGGCCGGGCCCGGCCCTGGAG**<u>A</u>**
<u>TG</u>GTCCCCGGCGCCGCGGGCTGGTGTTGTCTCGTGCTCTGGCTCCCCGCGTGCGTCGCGG
CCCACGGCTTCCGTATCCATGATTATTTGTACTTTCAAGTGCTGAGTCCTGGGGACATTC
GATACATCTTCACAGCCACACCTGCCAAGGACTTTGGTGGTATCTTTCACACAAGGTATG
AGCAGATTCACCTTGTCCCCGCTGAACCTCCAGAGGCCTGCGGGGAACTCAGCAACGGTT
TCTTCATCCAGGACCAGATTGCTCTGGTGGAGAGGGGGGGCTGCTCCTTCCTCTCCAAGA
CTCGGGTGGTCCAGGAGCACGGCGGGCGGGCGGTGATCATCTCTGACAACGCAGTTGACA
ATGACAGCTTCTACGTGGAGATGATCCAGGACAGTACCCAGCGCACAGCTGACATCCCCG
CCCTCTTCCTGCTCGGCCGAGACGGCTACATGATCCGCCGCTCTCTGGAACAGCATGGGC
TGCCATGGGCCATCATTTCCATCCCAGTCAATGTCACCAGCATCCCCACCTTTGAGCTGC
TGCAACCGCCCTGGACCTTCTGG**<u>TAG</u>**AAGAGTTTGTCCCACATTCCAGCCATAAGTGACT
CTGAGCTGGGAAGGGGAAACCCAGGAATTTTGCTACTTGGAATTTGGAGATAGCATCTGG
GGACAAGTGGAGCCAGGTAGAGGAAAAGGGTTTGGGCGTTGCTAGGCTGAAAGGGAAGCC
ACACCACTGGCCTTCCCTTCCCCAGGGCCCCCAAGGGTGTCTCATGCTACAAGAAGAGGC
AAGAGACAGGCCCCAGGGCTTCTGGCTAGAACCCGAAACAAAAGGAGCTGAAGGCAGGTG
GCCTGAGAGCCATCTGTGACCTGTCACACTCACCTGGCTCCAGCCTCCCCTACCCAGGGT
CTCTGCACAGTGACCTTCACAGCAGTTGTTGGAGTGGTTTAAAGAGCTGGTGTTTGGGGA
CTCAATAAACCCTCACTGACTTTTTAGCAATAAAGCTTCTCATCAGGGTTGCAAAAAAAA
AAAAAAAAAAAAAAAAAA

FIGURE 256

MVPGAAGWCCLVLWLPACVAAHGFRIHDYLYFQVLSPGDIRYIFTATPAKDFGGIFHTRY
EQIHLVPAEPPEACGELSNGFFIQDQIALVERGGCSFLSKTRVVQEHGGRAVIISDNAVD
NDSFYVEMIQDSTQRTADIPALFLLGRDGYMIRRSLEQHGLPWAIISIPVNVTSIPTFEL
LQPPWTFW

Signal peptide:
amino acids 1-20

FIGURE 257

CTCGCTTCTTCCTTCTGGATGGGGGCCCAGGGGGCCCAGGAGAGTATAAAGGCGATGTGG
AGGGTGCCCGGCACAACCAGACGCCCAGTCACAGGCGAGAGCCCTGGGATGCACCGGCCA
GAGGCCATGCTGCTGCTGCTCACGCTTGCCCTCCTGGGGGGCCCCACCTGGGCAGGGAAG
ATGTATGGCCCTGGAGGAGGCAAGTATTTCAGCACCACTGAAGACTACGACCATGAAATC
ACAGGGCTGCGGGTGTCTGTAGGTCTTCTCCTGGTGAAAAGTGTCCAGGTGAAACTTGGA
GACTCCTGGGACGTGAAACTGGGAGCCTTAGGTGGGAATACCCAGGAAGTCACCCTGCAG
CCAGGCGAATACATCACAAAAGTCTTTGTCGCCTTCCAAGCTTTCCTCCGGGGTATGGTC
ATGTACACCAGCAAGGACCGCTATTTCTATTTTGGGAAGCTTGATGGCCAGATCTCCTCT
GCCTACCCCAGCCAAGAGGGGCAGGTGCTGGTGGGCATCTATGGCCAGTATCAACTCCTT
GGCATCAAGAGCATTGGCTTTGAATGGAATTATCCACTAGAGGAGCCGACCACTGAGCCA
CCAGTTAATCTCACATACTCAGCAAACTCACCCGTGGGTCGCTAGGGTGGGGTATGGGGC
CATCCGAGCTGAGGCCATCTGTGTGGTGGTGGCTGATGGTACTGGAGTAACTGAGTCGGG
ACGCTGAATCTGAATCCACCAATAAATAAAGCTTCTGCAGAAAA

FIGURE 258

MHRPEAMLLLLTLALLGGPTWAGKMYGPGGGKYFSTTEDYDHEITGLRVSVGLLLVKSVQ
VKLGDSWDVKLGALGGNTQEVTLQPGEYITKVFVAFQAFLRGMVMYTSKDRYFYFGKLDG
QISSAYPSQEGQVLVGIYGQYQLLGIKSIGFEWNYPLEEPTTEPPVNLTYSANSPVGR

Signal peptide:
amino acids 1-22

FIGURE 259

CAGAC**ATG**GCTCAGTCACTGGCTCTGAGCCTCCTTATCCTGGTTCTGGCCTTTGGCATCC
CCAGGACCCAAGGCAGTGATGGAGGGGCTCAGGACTGTTGCCTCAAGTACAGCCAAAGGA
AGATTCCCGCCAAGGTTGTCCGCAGCTACCGGAAGCAGGAACCAAGCTTAGGCTGCTCCA
TCCCAGCTATCCTGTTCTTGCCCCGCAAGCGCTCTCAGGCAGAGCTATGTGCAGACCCAA
AGGAGCTCTGGGTGCAGCAGCTGATGCAGCATCTGGACAAGACACCATCCCCACAGAAAC
CAGCCCAGGGCTGCAGGAAGGACAGGGGGGCCTCCAAGACTGGCAAGAAAGGAAAGGGCT
CCAAAGGCTGCAAGAGGACTGAGCGGTCACAGACCCCTAAAGGGCCA**TAG**CCCAGTGAGC
AGCCTGGAGCCCTGGAGACCCCACCAGCCTCACCAGCGCTTGAAGCCTGAACCCAAGATG
CAAGAAGGAGGCTATGCTCAGGGGCCCTGGAGCAGCCACCCCATGCTGGCCTTGCCACAC
TCTTTCTCCTGCTTTAACCACCCCATCTGCATTCCCAGCTCTACCCTGCATGGCTGAGCT
GCCCACAGCAGGCCAGGTCCAGAGAGACCGAGGAGGGAGAGTCTCCCAGGGAGCATGAGA
GGAGGCAGCAGGACTGTCCCCTTGAAGGAGAATCATCAGGACCCTGGACCTGATACGGCT
CCCCAGTACACCCCACCTCTTCCTTGTAAATATGATTTATACCTAACTGAATAAAAAGCT
GTTCTGTCTTCCCNCCCA

FIGURE 260

MAQSLALSLLILVLAFGIPRTQGSDGGAQDCCLKYSQRKIPAKVVRSYRKQEPSLGCSIP
AILFLPRKRSQAELCADPKELWVQQLMQHLDKTPSPQKPAQGCRKDRGASKTGKKGKGSK
GCKRTERSQTPKGP

Important features of the protein:
Signal peptide:
amino acids 1-17

cAMP- and cGMP-dependent protein kinase phosphorylation site:
amino acids 67-71

N-myristoylation sites:
amino acids 17-23, 23-29, 27-33, 108-114, 118-124, 121-127

Amidation site:
amino acids 112-116

Small cytokines:
amino acids 51-91

FIGURE 261

GGGACTACAAGCCGCGCCGCGCTGCCGCTGGCCCCTCAGCAACCCTCGAC**ATG**GCGCTGA
GGCGGCCACCGCGACTCCGGCTCTGCGCTCGGCTGCCTGACTTCTTCCTGCTGCTGCTTT
TCAGGGGCTGCCTGATAGGGGCTGTAAATCTCAAATCCAGCAATCGAACCCCAGTGGTAC
AGGAATTTGAAAGTGTGGAACTGTCTTGCATCATTACGGATTCGCAGACAAGTGACCCCA
GGATCGAGTGGAAGAAAATTCAAGATGAACAAACCACATATGTGTTTTTTGACAACAAAA
TTCAGGGAGACTTGGCGGGTCGTGCAGAAATACTGGGGAAGACATCCCTGAAGATCTGGA
ATGTGACACGGAGAGACTCAGCCCTTTATCGCTGTGAGGTCGTTGCTCGAAATGACCGCA
AGGAAATTGATGAGATTGTGATCGAGTTAACTGTGCAAGTGAAGCCAGTGACCCCTGTCT
GTAGAGTGCCGAAGGCTGTACCAGTAGGCAAGATGGCAACACTGCACTGCCAGGAGAGTG
AGGGCCACCCCCGGCCTCACTACAGCTGGTATCGCAATGATGTACCACTGCCCACGGATT
CCAGAGCCAATCCCAGATTTCGCAATTCTTCTTTCCACTTAAACTCTGAAACAGGCACTT
TGGTGTTCACTGCTGTTCACAAGGACGACTCTGGGCAGTACTACTGCATTGCTTCCAATG
ACGCAGGCTCAGCCAGGTGTGAGGAGCAGGAGATGGAAGTCTATGACCTGAACATTGGCG
GAATTATTGGGGGGGTTCTGGTTGTCCTTGCTGTACTGGCCCTGATCACGTTGGGCATCT
GCTGTGCATACAGACGTGGCTACTTCATCAACAATAAACAGGATGGAGAAAGTTACAAGA
ACCCAGGGAAACCAGATGGAGTTAACTACATCCGCACTGACGAGGAGGGCGACTTCAGAC
ACAAGTCATCGTTTGTGATC**TGA**GACCCGCGGTGTGGCTGAGAGCGCACAGAGCGCACGT
GCACATACCTCTGCTAGAAACTCCTGTCAAGGCAGCGAGAGCTGATGCACTCGGACAGAG
CTAGACACTCATTCAGAAGCTTTTCGTTTTGGCCAAAGTTGACCACTACTCTTCTTACTC
TAACAAGCCACATGAATAGAAGAATTTTCCTCAAGATGGACCCGGTAAATATAACCACAA
GGAAGCGAAACTGGGTGCGTTCACTGAGTTGGGTTCCTAATCTGTTTCTGGCCTGATTCC
CGCATGAGTATTAGGGTGATCTTAAAGAGTTTGCTCACGTAAACGCCCGTGCTGGGCCCT
GTGAAGCCAGCATGTTCACCACTGGTCGTTCAGCAGCCACGACAGCACCATGTGAGATGG
CGAGGTGGCTGGACAGCACCAGCAGCGCATCCCGGCGGGAACCCAGAAAAGGCTTCTTAC
ACAGCAGCCTTACTTCATCGGCCCACAGACACCACCGCAGTTTCTTCTTAAAGGCTCTGC
TGATCGGTGTTGCAGTGTCCATTGTGGAGAAGCTTTTTGGATCAGCATTTTGTAAAAACA
ACCAAAATCAGGAAGGTAAATTGGTTGCTGGAAGAGGGATCTTGCCTGAGGAACCCTGCT
TGTCCAACAGGGTGTCAGGATTTAAGGAAAACCTTCGTCTTAGGCTAAGTCTGAAATGGT
ACTGAAATATGCTTTTCTATGGGTCTTGTTTATTTTATAAAATTTTACATCTAAATTTTT
GCTAAGGATGTATTTTGATTATTGAAAAGAAAATTTCTATTTAAACTGTAAATATATTGT
CATACAATGTTAAATAACCTATTTTTTTAAAAAAGTTCAACTTAAGGTAGAAGTTCCAAG
CTACTAGTGTTAAATTGGAAAATATCAATAATTAAGAGTATTTTACCCAAGGAATCCTCT
CATGGAAGTTTACTGTGATGTTCCTTTTCTCACACAAGTTTTAGCCTTTTTCACAAGGGA
ACTCATACTGTCTACACATCAGACCATAGTTGCTTAGGAAACCTTTAAAAATTCCAGTTA
AGCAATGTTGAAATCAGTTTGCATCTCTTCAAAAGAAACCTCTCAGGTTAGCTTTGAACT
GCCTCTTCCTGAGATGACTAGGACAGTCTGTACCCAGAGGCCACCCAGAAGCCCTCAGAT
GTACATACACAGATGCCAGTCAGCTCCTGGGGTTGCGCCAGGCGCCCCCGCTCTAGCTCA
CTGTTGCCTCGCTGTCTGCCAGGAGGCCCTGCCATCCTTGGGCCCTGGCAGTGGCTGTGT
CCCAGTGAGCTTTACTCACGTGGCCCTTGCTTCATCCAGCACAGCTCTCAGGTGGGCACT
GCAGGGACACTGGTGTCTTCCATGTAGCGTCCCAGCTTTGGGCTCCTGTAACAGACCTCT
TTTTGGTTATGGATGGCTCACAAAATAGGGCCCCCAATGCTATTTTTTTTTTTTAAGTTT
GTTTAATTATTTGTTAAGATTGTCTAAGGCCAAAGGCAATTGCGAAATCAAGTCTGTCAA
GTACAATAACATTTTTAAAAGAAAATGGATCCCACTGTTCCTCTTTGCCACAGAGAAAGC
ACCCAGACGCCACAGGCTCTGTCGCATTTCAAAACAAACCATGATGGAGTGGCGGCCAGT
CCAGCCTTTTAAAGAACGTCAGGTGGAGCAGCCAGGTGAAAGGCCTGGCGGGGAGGAAAG
TGAAACGCCTGAATCAAAAGCAGTTTTCTAATTTTGACTTTAAATTTTTCATCCGCCGGA

GACACTGCTCCCATTTGTGGGGGGACATTAGCAACATCACTCAGAAGCCTGTGTTCTTCA
AGAGCAGGTGTTCTCAGCCTCACATGCCCTGCCGTGCTGGACTCAGGACTGAAGTGCTGT
AAAGCAAGGAGCTGCTGAGAAGGAGCACTCCACTGTGTGCCTGGAGAATGGCTCTCACTA
CTCACCTTGTCTTTCAGCTTCCAGTGTCTTGGGTTTTTTATACTTTGACAGCTTTTTTTT
AATTGCATACATGAGACTGTGTTGACTTTTTTTAGTTATGTGAAACACTTTGCCGCAGGC
CGCCTGGCAGAGGCAGGAAATGCTCCAGCAGTGGCTCAGTGCTCCCTGGTGTCTGCTGCA
TGGCATCCTGGATGCTTAGCATGCAAGTTCCCTCCATCATTGCCACCTTGGTAGAGAGGG
ATGGCTCCCCACCCTCAGCGTTGGGGATTCACGCTCCAGCCTCCTTCTTGGTTGTCATAG
TGATAGGGTAGCCTTATTGCCCCCTCTTCTTATACCCTAAAACCTTCTACACTAGTGCCA
TGGGAACCAGGTCTGAAAAAGTAGAGAGAAGTGAAAGTAGAGTCTGGGAAGTAGCTGCCT
ATAACTGAGACTAGACGGAAAAGGAATACTCGTGTATTTTAAGATATGAATGTGACTCAA
GACTCGAGGCCGATACGAGGCTGTGATTCTGCCTTTGGATGGATGTTGCTGTACACAGAT
GCTACAGACTTGTACTAACACACCGTAATTTGGCATTTGTTTAACCTCATTTATAAAAGC
TTCAAAAAAACCCA

FIGURE 262

MALRRPPRLRLCARLPDFFLLLLFRGCLIGAVNLKSSNRTPVVQEFESVELSCIITDSQT
SDPRIEWKKIQDEQTTYVFFDNKIQGDLAGRAEILGKTSLKIWNVTRRDSALYRCEVVAR
NDRKEIDEIVIELTVQVKPVTPVCRVPKAVPVGKMATLHCQESEGHPRPHYSWYRNDVPL
PTDSRANPRFRNSSFHLNSETGTLVFTAVHKDDSGQYYCIASNDAGSARCEEQEMEVYDL
NIGGIIGGVLVVLAVLALITLGICCAYRRGYFINNKQDGESYKNPGKPDGVNYIRTDEEG
DFRHKSSFVI

Important features of the protein:
Signal peptide:
amino acids 1-30

Transmembrane domain:
amino acids 243-263

N-glycosylation sites:
amino acids 104-107, 192-195

cAMP- and cGMP-dependent protein kinase phosphorylation site:
amino acids 107-110

Casein kinase II phosphorylation site:
amino acids 106-109, 296-299

Tyrosine kinase phosphorylation site:
amino acids 69-77

N-myristoylation sites:
amino acids 26-31, 215-220, 226-231, 243-248, 244-249, 262-267

FIGURE 263

CCAGGACCAGGGCGCACCGGCTCAGCCTCTCACTTGTCAGAGGCCGGGGAAGAGAAGCAA
AGCGCAACGGTGTGGTCCAAGCCGGGGCTTCTGCTTCGCCTCTAGGACATACACGGGACC
CCCTAACTTCAGTCCCCCAAACGCGCACCCTCGAAGTCTTGAACTCCAGCCCCGCACATC
CACGCGCGGCACAGGCGCGGCAGGCGGCAGGTCCCGGCCGAAGGCGATGCGCGCAGGGGG
TCGGGCAGCTGGGCTCGGGCGGCGGGAGTAGGGCCCGGCAGGGAGGCAGGGAGGCTGCAT
ATTCAGAGTCGCGGGCTGCGCCCTGGCAGAGGCCGCCCTCGCTCCACGCAACACCTGCT
GCTGCCACCGCGCCGCG<u>ATG</u>AGCCGCGTGGTCTCGCTGCTGCTGGGCGCCGCGCTGCTCT
GCGGCCACGGAGCCTTCTGCCGCCGCGTGGTCAGCGGCCAAAAGGTGTGTTTTGCTGACT
TCAAGCATCCCTGCTACAAAATGGCCTACTTCCATGAACTGTCCAGCCGAGTGAGCTTTC
AGGAGGCACGCCTGGCTTGTGAGAGTGAGGGAGGAGTCCTCCTCAGCCTTGAGAATGAAG
CAGAACAGAAGTTAATAGAGAGCATGTTGCAAAACCTGACAAAACCCGGGACAGGGATTT
CTGATGGTGATTTCTGGATAGGGCTTTGGAGGAATGGAGATGGCAAACATCTGGTGCCT
GCCCAGATCTCTACCAGTGGTCTGATGGAAGCAATTCCCAGTACCGAAACTGGTACACAG
ATGAACCTTCCTGCGGAAGTGAAAAGTGTGTTGTGATGTATCACCAACCAACTGCCAATC
CTGGCCTTGGGGGTCCCTACCTTTACCAGTGGAATGATGACAGGTGTAACATGAAGCACA
ATTATATTTGCAAGTATGAACCAGAGATTAATCCAACAGCCCCTGTAGAAAAGCCTTATC
TTACAAATCAACCAGGAGACACCCATCAGAATGTGGTTGTTACTGAAGCAGGTATAATTC
CCAATCTAATTTATGTTGTTATACCAACAATACCCCTGCTCTTACTGATACTGGTTGCTT
TTGGAACCTGTTGTTTCCAGATGCTGCATAAAAGTAAAGGAAGAACAAAAACTAGTCCAA
ACCAGTCTACACTGTGGATTTCAAAGAGTACCAGAAAAGAAAGTGGCATGGAAGTA<u>TAA</u>T
AACTCATTGACTTGGTTCCAGAATTTTGTAATTCTGGATCTGTATAAGGAATGGCATCAG
AACAATAGCTTGGAATGGCTTGAAATCACAAAGGATCTGCAAGATGAACTGTAAGCTCCC
CCTTGAGGCAAATATTAAAGTAATTTTTATATGTCTATTATTTCATTTAAAGAATATGCT
GTGCTAATAATGGAGTGAGACATGCTTATTTTGCTAAAGGATGCACCCAAACTTCAAACT
TCAAGCAAATGAAATGGACAATGCAGATAAAGTTGTTATCAACACGTCGGGAGTATGTGT
GTTAGAAGCAATTCCTTTTATTTCTTTCACCTTTCATAAGTTGTTATCTAGTCAATGTAA
TGTATATTGTATTGAAATTTACAGTGTGCAAAAGTATTTTACCTTTGCATAAGTGTTTGA
TAAAAATGAACTGTTCTAATATTTATTTTTATGGCATCTCATTTTTCAATACATGCTCTT
TTGATTAAAGAAACTTATTACTGTTGTCAACTGAATTCACACACACACAAATATAGTACC
ATAGAAAAAGTTTGTTTTCTCGAAATAATTCATCTTTCAGCTTCTCTGCTTTTGGTCAAT
GTCTAGGAAATCTCTTCAGAAATAAGAAGCTATTTCATTAAGTGTGATATAAACCTCCTC
AAACATTTTACTTAGAGGCAAGGATTGTCTAATTTCAATTGTGCAAGACATGTGCCTTAT
AATTATTTTTAGCTTAAAATTAAACAGATTTTGTAATAATGTAACTTTGTTAATAGGTGC
ATAAACACTAATGCAGTCAATTTGAACAAAAGAAGTGACATACACAATATAAATCATATG
TCTTCACACGTTGCCTATATAATGAGAAGCAGCTCTCTGAGGGTTCTGAAATCAATGTGG
TCCCTCTCTTGCCCACTAAACAAAGATGGTTGTTCGGGGTTTGGGATTGACACTGGAGGC
AGATAGTTGCAAAGTTAGTCTAAGGTTTCCCTAGCTGTATTTAGCCTCTGACTATATTAG
TATACAAAGAGGTCATGTGGTTGAGACCAGGTGAATAGTCACTATCAGTGTGGAGACAAG
CACAGCACACAGACATTTTAGGAAGGAAAGGAACTACGAAATCGTGTGAAAATGGGTTGG
AACCCATCAGTGATCGCATATTCATTGATGAGGGTTTGCTTGAGATAGAAAATGGTGGCT
CCTTTCTGTCTTATCTCCTAGTTTCTTCAATGCTTACGCCTTGTTCTTCTCAAGAGAAAG
TTGTAACTCTCTGGTCTTCATATGTCCCTGTGCTCCTTTTAACCAAATAAAGAGTTCTTG
TTTCTGGGGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 264

MSRVVSLLLGAALLCGHGAFCRRVVSGQKVCFADFKHPCYKMAYFHELSSRVSFQEARLA
CESEGGVLLSLENEAEQKLIESMLQNLTKPGTGISDGDFWIGLWRNGDGQTSGACPDLYQ
WSDGSNSQYRNWYTDEPSCGSEKCVVMYHQPTANPGLGGPYLYQWNDDRCNMKHNYICKY
EPEINPTAPVEKPYLTNQPGDTHQNVVVTEAGIIPNLIYVVIPTIPLLLLILVAFGTCCF
QMLHKSKGRTKTSPNQSTLWISKSTRKESGMEV

Important features of the protein:
Signal peptide:
amino acids 1-21

Transmembrane domain:
amino acids 214-235

N-glycosylation sites:
amino acids 86-89 and 255-258

cAMP- and cGMP-dependent protein kinase phosphorylation site:
amino acids 266-269

N-myristoylation sites:
amino acids 27-32, 66-71, 91-96, 93-98, 102-107, 109-114, 140-145 and 212-217

FIGURE 265

GGAGA**<u>ATG</u>**GAGAGAGCAGTGAGAGTGGAGTCCGGGGTCCTGGTCGGGGTGGTCTGTCTGC
TCCTGGCATGCCCTGCCACAGCCACTGGGCCCGAAGTTGCTCAGCCTGAAGTAGACACCA
CCCTGGGTCGTGTGCGAGGCCGGCAGGTGGGCGTGAAGGGCACAGACCGCCTTGTGAATG
TCTTTCTGGGCATTCCATTTGCCCAGCCGCCACTGGGCCCTGACCGGTTCTCAGCCCCAC
ACCCAGCACAGCCCTGGGAGGGTGTGCGGGATGCCAGCACTGCGCCCCCAATGTGCCTAC
AAGACGTGGAGAGCATGAACAGCAGCAGATTTGTCCTCAACGGAAAACAGCAGATCTTCT
CCGTTTCAGAGGACTGCCTGGTCCTCAACGTCTATAGCCCAGCTGAGGTCCCCGCAGGGT
CCGGTAGGCCGGTCATGGTATGGGTCCATGGAGGCGCTCTGATAACTGGCGCTGCCACCT
CCTACGATGGATCAGCTCTGGCTGCCTATGGGGATGTGGTCGTGGTTACAGTCCAGTACC
GCCTTGGGGTCCTTGGCTTCTTCAGCACTGGAGATGAGCATGCACCTGGCAACCAGGGCT
TCCTAGATGTGGTAGCTGCTTTGCGCTGGGTGCAAGAAAACATCGCCCCCTTCGGGGGTG
ACCTCAACTGTGTCACTGTCTTTGGTGGATCTGCCGGTGGGAGCATCATCTCTGGCCTGG
TCCTGTCCCCAGTGGCTGCAGGGCTGTTCCACAGAGCCATCACACAGAGTGGGGTCATCA
CCACCCCAGGGATCATCGACTCTCACCCTTGGCCCCTAGCTCAGAAAATCGCAAACACCT
TGGCCTGCAGCTCCAGCTCCCCGGCTGAGATGGTGCAGTGCCTTCAGCAGAAAGAAGGAG
AAGAGCTGGTCCTTAGCAAGAAGCTGAAAAATACTATCTATCCTCTCACCGTTGATGGCA
CTGTCTTCCCCAAAAGCCCCAAGGAACTCCTGAAGGAGAAGCCCTTCCACTCTGTGCCCT
TCCTCATGGGTGTCAACAACCATGAGTTCAGCTGGCTCATCCCCAGGGGCTGGGGTCTCC
TGGATACAATGGAGCAGATGAGCCGGGAGGACATGCTGGCCATCTCAACACCCGTCTTGA
CCAGTCTGGATGTGCCCCCTGAGATGATGCCCACCGTCATAGATGAATACCTAGGAAGCA
ACTCGGACGCACAAGCCAAATGCCAGGCGTTCCAGGAATTCATGGGTGACGTATTCATCA
ATGTTCCCACCGTCAGTTTTTCAAGATACCTTCGAGATTCTGGAAGCCCTGTCTTTTTCT
ATGAGTTCCAGCATCGACCCAGTTCTTTTGCGAAGATCAAACCTGCCTGGGTGAAGGCTG
ATCATGGGGCCGAGGGTGCTTTTGTGTTCGGAGGTCCCTTCCTCATGGACGAGAGCTCCC
GCCTGGCCTTTCCAGAGGCCACAGAGGAGGAGAAGCAGCTAAGCCTCACCATGATGGCCC
AGTGGACCCACTTTGCCCGGACAGGGGACCCCAATAGCAAGGCTCTGCCTCCTTGGCCCC
AATTCAACCAGGCGGAACAATATCTGGAGATCAACCCAGTGCCACGGGCCGGACAGAAGT
TCAGGGAGGCCTGGATGCAGTTCTGGTCAGAGACGCTCCCCAGCAAGATACAACAGTGGC
ACCAGAAGCAGAAGAACAGGAAGGCCCAGGAGGACCTC**<u>TGA</u>**GGCCAGGCCTGAACCTTCT
TGGCTGGGGCAAACCACTCTTCAAGTGGTGGCAGAGTCCCAGCACGGCAGCCCGCCTCTC
CCCCTGCTGAGACTTTAATCTCCACCAGCCCTTAAAGTGTCGGCCGCTCTGTGACTGGAG
TTATGCTCTTTTGAAATGTCACAAGGCCGCCTCCCACCTCTGGGGCATTGTACAAGTTCT
TCCCTCTCCCTGAAGTGCCTTTCCTGCTTTCTTCGTGGTAGGTTCTAGCACATTCCTCTA
GCTTCCTGGAGGACTCACTCCCCAGGAAGCCTTCCCTGCCTTCTCTGGGCTGTGCGGCCC
CGAGTCTGCGTCCATTAGAGCACAGTCCACCCGAGGCTAGCACCGTGTCTGTGTCTGTCT
CCCCCTCAGAGGAGCTCTCTCAAAATGGGGATTAGCCTAACCCCACTCTGTCACCCACAC
CAGGATCGGGTGGGACCTGGAGCTAGGGGGTGTTTGCTGAGTGAGTGAGTGAAACACAGA
ATATGGGAATGGCAGCTGCTGAACTTGAACCCAGAGCCTTCAGGTGCCAAAGCCATACTC
AGGCCCCCACCGACATTGTCCACCCTGGCCAGAAGGGTGCATGCCAATGGCAGAGACCTG
GGATGGGAGAAGTCCTGGGGCGCCAGGGGATCCAGCCTAGAGCAGACCTTAGCCCCTGAC
TAAGGCCTCAGACTAGGGCGGGAGGGGTCTCCTCCTCTCTGCTGCCCAGTCCTGGCCCCT
GCACAAGACAACAGAATCCATCAGGGCCATGAGTGTCACCCAGACCTGACCCTCACCAAT
TCCAGCCCCTGACCCTCAGGACGCTGGATGCCAGCTCCCAGCCCCAGTGCCGGGTCCTCC
CTCCCTTCCTGGCTTGGGGAGACCAGTTTCTGGGGAGCTTCCAAGAGCACCCACCAAGAC
ACAGCAGGACAGGCCAGGGGAGGGCATCTGGACCAGGGCATCCGTCGGCTATTGTCACA
GAGAAAAGAAGAGACCCACCCACTCGGGCTGCAAAAGGTGAAAAGCACCAAGAGGTTTTC

AGATGGAAGTGAGAGGTGACAGTGTGCTGGCAGCCCTCACAGCCCTCGCTTGCTCTCCCT
GCCGCCTCTGCCTGGGCTCCCACTTTGGCAGCACTTGAGGAGCCCTTCAACCCGCCGCTG
CACTGTAGGAGCCCCTTTCTGGGCTGGCCAAGGCCGGAGCCAGCTCCCTCAGCTTGCGGG
GAGGTGCGGAGGGAGAGGGGCGGGCAGGAACCGGGGCTGCGCGCAGCGCTTGCGGGCCAG
AGTGAGTTCCGGGTGGGCGTGGGCTCGGCGGGGCCCCACTCAGAGCAGCTGGCCGGCCCC
AGGCAGTGAGGGCCTTAGCACCTGGGCCAGCAGCTGCTGTGCTCGATTTCTCGCTGGGCC
TTAGCTGCCTCCCCGCGGGGCAGGGCTCGGGACCTGCAGCCCTCCATGCCTGACCCTCCC
CCCACCCCCCGTGGGCTCCTGTGCGGCCGGAGCCTCCCCAAGGAGCGCCGCCCCCTGCTC
CACAGCGCCCAGTCCCATCGACCACCCAAGGGCTGAGGAGTGCGGGTGCACAGCGCGGGA
CTGGCAGGCAGCTCCACCTGCTGCCCCAGTGCTGGATCCACTGGGTGAAGCCAGCTGGGC
TCCTGAGTCTGGTGGGGACTTGGAGAACCTTTATGTCTAGCTAAGGGATTGTAAATACAC
CGATGGGCACTCTGTATCTAGCTCAAGGTTTGTAAACACACCAATCAGCACCCTGTGTCT
AGCTCAGTGTTTGTGAATGCACCAATCCACACTCTGTATCTGGCTACTCTGGTGGGGACT
TGGAGAACCTTTGTGTCCACACTCTGTATCTAGCTAATCTAGTGGGGATGTGGAGAACCT
TTGTGTCTAGCTCAGGGATCGTAAACGCACCAATCAGCACCCTGTCAAAACAGACCACTT
GACTCTCTGTAAAATGGACCAATCAGCAGGATGTGGGTGGGGCGAGACAAGAGAATAAAA
GCAGGCTGCCTGAGCCAGCAGTGACAACCCCCCTCGGGTCCCCTCCCACGCCGTGGAAGC
TTTGTTCTTTCGCTCTTTGCAATAAATCTTGCTACTGCCCAAAA

FIGURE 266

MERAVRVESGVLVGVVCLLLACPATATGPEVAQPEVDTTLGRVRGRQVGVKGTDRLVNVF
LGIPFAQPPLGPDRFSAPHPAQPWEGVRDASTAPPMCLQDVESMNSSRFVLNGKQQIFSV
SEDCLVLNVYSPAEVPAGSGRPVMVWVHGGALITGAATSYDGSALAAYGDVVVVTVQYRL
GVLGFFSTGDEHAPGNQGFLDVVAALRWVQENIAPFGGDLNCVTVFGGSAGGSIISGLVL
SPVAAGLFHRAITQSGVITTPGIIDSHPWPLAQKIANTLACSSSSPAEMVQCLQQKEGEE
LVLSKKLKNTIYPLTVDGTVFPKSPKELLKEKPFHSVPFLMGVNNHEFSWLIPRGWGLLD
TMEQMSREDMLAISTPVLTSLDVPPEMMPTVIDEYLGSNSDAQAKCQAFQEFMGDVFINV
PTVSFSRYLRDSGSPVFFYEFQHRPSSFAKIKPAWVKADHGAEGAFVFGGPFLMDESSRL
AFPEATEEEKQLSLTMMAQWTHFARTGDPNSKALPPWPQFNQAEQYLEINPVPRAGQKFR
EAWMQFWSETLPSKIQQWHQKQKNRKAQEDL

Important features of the protein:
Signal peptide:
amino acids 1-27

Transmembrane domain:
amino acids 226-245

N-glycosylation site:
amino acids 105-109

N-myristoylation sites:
amino acids 10-16, 49-55, 62-68, 86-92, 150-156, 155-161, 162-168, 217-223, 227-233, 228-234, 232-238, 262-268, 357-363, 461-467

Prokaryotic membrane lipoprotein lipid attachment site:
amino acids 12-23

Carboxylesterases type-B serine active site:
amino acids 216-232

FIGURE 267

TGTCGCCTGGCCCTCGCC**ATG**CAGACCCCGCGAGCGTCCCCTCCCCGCCCGGCCCTCCTG
CTTCTGCTGCTGCTACTGGGGGGCGCCCACGGCCTCTTTCCTGAGGAGCCGCCGCCGCTT
AGCGTGGCCCCCAGGGACTACCTGAACCACTATCCCGTGTTTGTGGGCAGCGGGCCCGGA
CGCCTGACCCCCGCAGAAGGTGCTGACGACCTCAACATCCAGCGAGTCCTGCGGGTCAAC
AGGACGCTGTTCATTGGGGACAGGGACAACCTCTACCGCGTAGAGCTGGAGCCCCCCACG
TCCACGGAGCTGCGGTACCAGAGGAAGCTGACCTGGAGATCTAACCCCAGCGACATAAAC
GTGTGTCGGATGAAGGGCAAACAGGAGGGCGAGTGTCGAAACTTCGTAAAGGTGCTGCTC
CTTCGGGACGAGTCCACGCTCTTTGTGTGCGGTTCCAACGCCTTCAACCCGGTGTGCGCC
AACTACAGCATAGACACCCTGCAGCCCGTCGGAGACAACATCAGCGGTATGGCCCGCTGC
CCGTACGACCCCAAGCACGCCAATGTTGCCCTCTTCTCTGACGGGATGCTCTTCACAGCT
ACTGTTACCGACTTCCTAGCCATTGATGCTGTCATCTACCGCAGCCTCGGGGACAGGCCC
ACCCTGCGCACCGTGAAACATGACTCCAAGTGGTTCAAAGAGCCTTACTTTGTCCATGCG
GTGGAGTGGGGCAGCCATGTCTACTTCTTCTTCCGGGAGATTGCGATGGAGTTTAACTAC
CTGGAGAAGGTGGTGGTGTCCCGCGTGGCCCGAGTGTGCAAGAACGACGTGGGAGGCTCC
CCCCGCGTGCTGGAGAAGCAGTGGACGTCCTTCCTGAAGGCGCGGCTCAACTGCTCTGTA
CCCGGAGACTCCCATTTCTACTTCAACGTGCTGCAGGCTGTCACGGGCGTGGTCAGCCTC
GGGGGCCGGCCCGTGGTCCTGGCCGTTTTTCCACGCCCAGCAACAGCATCCCTGGCTCG
GCTGTCTGCGCCTTTGACCTGACACAGGTGGCAGCTGTGTTTGAAGGCCGCTTCCGAGAG
CAGAAGTCCCCCGAGTCCATCTGGACGCCGGTGCCGGAGGATCAGGTGCCTCGACCCCGG
CCCGGGTGCTGCGCAGCCCCCGGGATGCAGTACAATGCCTCCAGCGCCTTGCCGGATGAC
ATCCTCAACTTTGTCAAGACCCACCCTCTGATGGACGAGGCGGTGCCCTCGCTGGGCCAT
GCGCCCTGGATCCTGCGGACCCTGATGAGGCACCAGCTGACTCGAGTGGCTGTGGACGTG
GGAGCCGGCCCCTGGGGCAACCAGACCGTTGTCTTCCTGGGTTCTGAGGCGGGGACGGTC
CTCAAGTTCCTCGTCCGGCCCAATGCCAGCACCTCAGGGACGTCTGGGCTCAGTGTCTTC
CTGGAGGAGTTTGAGACCTACCGGCCGGACAGGTGTGGACGGCCCGGCGGTGGCGAGACA
GGGCAGCGGCTGCTGAGCTTGGAGCTGGACGCAGCTTCGGGGGGCCTGCTGGCTGCCTTC
CCCCGCTGCGTGGTCCGAGTGCCTGTGGCTCGCTGCCAGCAGTACTCGGGGTGTATGAAG
AACTGTATCGGCAGTCAGGACCCCTACTGCGGGTGGGCCCCCGACGGCTCCTGCATCTTC
CTCAGCCCGGGCACCAGAGCCGCCTTTGAGCAGGACGTGTCCGGGGCCAGCACCTCAGGC
TTAGGGGACTGCACAGGACTCCTGCGGGCCAGCCTCTCCGAGGACCGCGCGGGGCTGGTG
TCGGTGAACCTGCTGGTAACGTCGTCGGTGGCGGCCTTCGTGGTGGGAGCCGTGGTGTCC
GGCTTCAGCGTGGGCTGGTTCGTGGGCCTCCGTGAGCGGCGGGAGCTGGCCCGGCGCAAG
GACAAGGAGGCCATCCTGGCGCACGGGGCGGGCGAGGCGGTGCTGAGCGTCAGCCGCCTG
GGCGAGCGCAGGGCGCAGGGTCCCGGGGGCCGGGGCGGAGGCGGTGGCGGTGGCGCCGGG
GTTCCCCCGGAGGCCCTGCTGGCGCCCCTGATGCAGAACGGCTGGGCCAAGGCCACGCTG
CTGCAGGGCGGGCCCCACGACCTGGACTCGGGGCTGCTGCCCACGCCCGAGCAGACGCCG
CTGCCGCAGAAGCGCCTGCCCACTCCGCACCCGCACCCCCACGCCCTGGGCCCCCGCGCC
TGGGACCACGGCCACCCCCTGCTCCCGGCCTCCGCTTCATCCTCCCTCCTGCTGCTGGCG
CCCGCCCGGGCCCCCGAGCAGCCCCCCGCGCCTGGGGAGCCGACCCCCGACGGCCGCCTC
TATGCTGCCCGGCCCGGCCGCGCCTCCCACGGCGACTTCCCGCTCACCCCCCACGCCAGC
CCGGACCGCCGGCGGGTGGTGTCCGCGCCCACGGGCCCCTTGGACCCAGCCTCAGCCGCC
GATGGCCTCCCGCGGCCCTGGAGCCCGCCCCCGACGGGCAGCCTGAGGAGGCCACTGGGC
CCCCACGCCCCTCCGGCCGCCACCCTGCGCCGCACCCACACGTTCAACAGCGGCGAGGCC
CGGCCTGGGGACCGCCACCGCGGCTGCCACGCCCGGCCGGGCACAGACTTGGCCCACCTC
CTCCCCTATGGGGGGGCGGACAGGACTGCGCCCCCCGTGCCC**TAG**GCCGGGGGCCCCCCG
ATGCCTTGGCAGTGCCAGCCACGGGAACCAGGAGCGAGAGACGGTGCCAGAACGCCGGGG
CCCGGGGCAACTCCGAGTGGGTGCTCAAGTCCCCCCCGCGACCCACCCGCGGAGTGGGGG

GCCCCCTCCGCCACAAGGAAGCACAACCAGCTCGCCCTCCCCCTACCCGGGGCCGCAGGA
CGCTGAGACGGTTTGGGGGTGGGTGGGCGGGAGGACTTTGCTATGGATTTGAGGTTGACC
TTATGCGCGTAGGTTTTGGTTTTTTTTTGCAGTTTTGGTTTCTTTTGCGGTTTTCTAACC
AATTGCACAACTCCGTTCTCGGGGTGGCGGCAGGCAGGGGAGGCTTGGACGCCGGTGGGG
AATGGGGGGCCACAGCTGCAGACCTAAGCCCTCCCCCACCCCTGGAAAGGTCCCTCCCCA
ACCCAGGCCCCTGGCGTGTGTGGGTGTGCGTGCGTGTGCGTGCCGTGTTCGTGTGCAAGG
GGCCGGGGAGGTGGGCGTGTGTGTGCGTGCCAGCGAAGGCTGCTGTGGGCGTGTGTGTCA
AGTGGGCCACGCGTGCAGGGTGTGTGTCCACGAGCGACGATCGTGGTGGCCCCAGCGGCC
TGGGCGTTGGCTGAGCCGACGCTGGGGCTTCCAGAAGGCCCGGGGGTCTCCGAGGTGCCG
GTTAGGAGTTTGAACCCCCCCCACTCTGCAGAGGGAAGCGGGGACAATGCCGGGGTTTCA
GGCAGGAGACACGAGGAGGGCCTGCCCGGAAGTCACATCGGCAGCAGCTGTCTAAAGGGC
TTGGGGGCCTGGGGGGCGGCGAAGGTGGGTGGGGCCCCTCTGTAAATACGGCCCCAGGGT
GGTGAGAGAGTCCCATGCCACCCGTCCCCTTGTGACCTCCCCCCTATGACCTCCAGCTGA
CCATGCATGCCACGTGGCTGGCTGGGTCCTCTGCCCTCTTTGGAGTTTGCCTCCCCCAGC
CCCCTCCCCATCAATAAAACTCTGTTTACAACCAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 268

MQTPRASPPRPALLLLLLLLGGAHGLFPEEPPPLSVAPRDYLNHYPVFVGSGPGRLTPAE
GADDLNIQRVLRVNRTLFIGDRDNLYRVELEPPTSTELRYQRKLTWRSNPSDINVCRMKG
KQEGECRNFVKVLLLRDESTLFVCGSNAFNPVCANYSIDTLQPVGDNISGMARCPYDPKH
ANVALFSDGMLFTATVTDFLAIDAVIYRSLGDRPTLRTVKHDSKWFKEPYFVHAVEWGSH
VYFFFREIAMEFNYLEKVVVSRVARVCKNDVGGSPRVLEKQWTSFLKARLNCSVPGDSHF
YFNVLQAVTGVVSLGGRPVVLAVFSTPSNSIPGSAVCAFDLTQVAAVFEGRFREQKSPES
IWTPVPEDQVPRPRPGCCAAPGMQYNASSALPDDILNFVKTHPLMDEAVPSLGHAPWILR
TLMRHQLTRVAVDVGAGPWGNQTVVFLGSEAGTVLKFLVRPNASTSGTSGLSVFLEEFET
YRPDRCGRPGGGETGQRLLSLELDAASGGLLAAFPRCVVRVPVARCQQYSGCMKNCIGSQ
DPYCGWAPDGSCIFLSPGTRAAFEQDVSGASTSGLGDCTGLLRASLSEDRAGLVSVNLLV
TSSVAAFVVGAVVSGFSVGWFVGLRERRELARRKDKEAILAHGAGEAVLSVSRLGERRAQ
GPGGRGGGGGGGAGVPPEALLAPLMQNGWAKATLLQGGPHDLDSGLLPTPEQTPLPQKRL
PTPHPHPHALGPRAWDHGHPLLPASASSSLLLLAPARAPEQPPAPGEPTPDGRLYAARPG
RASHGDFPLTPHASPDRRRVVSAPTGPLDPASAADGLPRPWSPPPTGSLRRPLGPHAPPA
ATLRRTHTFNSGEARPGDRHRGCHARPGTDLAHLLPYGGADRTAPPVP

Important features of the protein:
Signal peptide:
amino acids 1-25

Transmembrane domains:
amino acids 318-339, 598-617

N-glycosylation sites.
amino acids 74-78, 155-159, 167-171, 291-295, 386-390, 441-445, 462-466

Glycosaminoglycan attachment sites:
amino acids 51-55, 573-577

cAMP- and cGMP-dependent protein kinase phosphorylation site:
amino acids 102-106

N-myristoylation sites:
amino acids 21-27, 50-56, 189-195, 333-339, 382-388, 448-454, 490-496, 491-497, 508-514, 509-515, 531-537, 558-564, 569-575, 574-580, 580-586, 610-616, 643-649, 663-669, 666-672, 667-673, 668-674, 669-675, 670-676, 868-874, 879-885

FIGURE 269

ATCTGAGTGAGCTAACTGACACAATGAAACTGTCAGGCATGTTTCTGCTCCTCTCTCTGG
CTCTTTTCTGCTTTTTAACAGGTGTCTTCAGTCAGGGAGGACAGGTTGACTGTGGTGAGT
TCCAGGACCCCAAGGTCTACTGCACTCGGGAATCTAACCCACACTGTGGCTCTGATGGCC
AGACATATGGCAATAAATGTGCCTTCTGTAAGGCCATAGTGAAAAGTGGTGGAAAGATTA
GCCTAAAGCATCCTGGAAAATGCTGAGTTAAAGCCAATGTTTCTTGGTGACTTGCCAGCT
TTTGCAGCCTTCTTTTCTCACTTCTGCTTATACTTTTGCTGGTGGATTCCTTTAATTCAT
AAAGACATACCTACTCTGCCTGGGTCTTGAGGAGTTCAATGTATGTCTATTTCTCTTGAT
TCACTTGTCAATAAAGTACATTCTGCAAAAGCAAAAA

FIGURE 270

MKLSGMFLLLSLALFCFLTGVFSQGGQVDCGEFQDPKVYCTRESNPHCGSDGQTYGNKCA
FCKAIVKSGGKISLKHPGKC

Important features of the protein:
Signal peptide:
amino acids 1-23

N-myristoylation sites:
amino acids 26-32, 52-58, 56-62, 69-75

Kazal serine protease inhibitors family signature:
amino acids 40-63

FIGURE 271

AACTTCTAC**ATG**GGCCTCCTGCTGCTGGTGCTCTTCCTCAGCCTCCTGCCGGTGGCCTAC
ACCATCATGTCCCTCCCACCCTCCTTTGACTGCGGGCCGTTCAGGTGCAGAGTCTCAGTT
GCCCGGGAGCACCTCCCCTCCCGAGGCAGTCTGCTCAGAGGGCCTCGGCCCAGAATTCCA
GTTCTGGTTTCATGCCAGCCTGTAAAAGGCCATGGAACTTTGGGTGAATCACCGATGCCA
TTTAAGAGGGTTTTCTGCCAGGATGGAAATGTTAGGTCGTTCTGTGTCTGCGCTGTTCAT
TTCAGTAGCCACCAGCCACCTGTGGCCGTTGAGTGCTTGAAA**TGA**GGAACTGAGAAAATT
AATTTCTCATGTATTTTTCTCATTTATTTATTAATTTTTAACTGATAGTTGTACATATTT
GGGGGTACATGTGATATTTGGATACATGTATACAATATATAATGATCAAATCAGGGTAAC
TGGGATATCCATCACATCAAACATTTATTTTTTATTCTTTTTAGACAGAGTCTCACTCTG
TCACCCAGGCTGGAGTGCAGTGGTGCCATCTCAGCTTACTGCAACCTCTGCCTGCCAGGT
TCAAGCGATTCTCATGCCTCCACCTCCCAAGTAGCTGGGACTACAGGCATGCACCACAAT
GCCCAACTAATTTTTGTATTTTTAGTAGAGACGGGGTTTTGCCATGTTGCCCAGGCTGGC
CTTGAACTCCTGGCCTCAAACAATCCACTTGCCTCGGCCTCCCAAAGTGTTATGATTACA
GGCGTGAGCCACCGTGCCTGGCCTAAACATTTATCTTTTCTTTGTGTTGGGAACTTTGAA
ATTATACAATGAATTATTGTTAACTGTCATCTCCCTGCTGTGCTATGGAACACTGGGACT
TCTTCCCTCTATCTAACTGTATATTTGTACCAGTTAACCAACCGTACTTCATCCCCACTC
CTCTCTATCCTTCCCAACCTCTGATCACCTCATTCTACTCTCTACCTCCATGAGATCCAC
TTTTTTAGCTCCCACATGTGAGTAAGAAAATGCAATATTTGTCTTTCTGTGCCTGGCTTA
TTTCACTTAACATAATGACTTCCTGTTCCATCCATGTTGCTGCAAATGACAGGATTTCGT
TCTTAATTTCAATTAAAATAACCACACATGGCAAAAA

FIGURE 272

MGLLLLVLFLSLLPVAYTIMSLPPSFDCGPFRCRVSVAREHLPSRGSLLRGPRPRIPVLV
SCQPVKGHGTLGESPMPFKRVFCQDGNVRSFCVCAVHFSSHQPPVAVECLK

Important features of the protein:
Signal peptide:
amino acids 1-18

N-myristoylation site:
amino acids 86-92

Zinc carboxypeptidases, zinc-binding region 2 signature:
amino acids 68-79

FIGURE 273

TTCTGAAGTAACGGAAGCTACCTTGTATAAAGACCTCAACACTGCTGACCATGATCAGCG
CAGCCTGGAGCATCTTCCTCATCGGGACTAAAATTGGGCTGTTCCTTCAAGTAGCACCTC
TATCAGTTATGGCTAAATCCTGTCCATCTGTGTGTCGCTGCGATGCGGGTTTCATTTACT
GTAATGATCGCTTTCTGACATCCATTCCAACAGGAATACCAGAGGATGCTACAACTCTCT
ACCTTCAGAACAACCAAATAAATAATGCTGGGATTCCTTCAGATTTGAAAAACTTGCTGA
AAGTAGAAAGAATATACCTATACCACAACAGTTTAGATGAATTTCCTACCAACCTCCCAA
AGTATGTAAAAGAGTTACATTTGCAAGAAAATAACATAAGGACTATCACTTATGATTCAC
TTTCAAAAATTCCCTATCTGGAAGAATTACATTTAGATGACAACTCTGTCTCTGCAGTTA
GCATAGAAGAGGGAGCATTCCGAGACAGCAACTATCTCCGACTGCTTTTCCTGTCCCGTA
ATCACCTTAGCACAATTCCCTGGGGTTTGCCCAGGACTATAGAAGAACTACGCTTGGATG
ATAATCGCATATCCACTATTTCATCACCATCTCTTCAAGGTCTCACTAGTCTAAAACGCC
TGGTTCTAGATGGAAACCTGTTGAACAATCATGGTTTAGGTGACAAAGTTTTCTTCAACC
TAGTTAATTTGACAGAGCTGTCCCTGGTGCGGAATTCCCTGACTGCTGCACCAGTAAACC
TTCCAGGCACAAACCTGAGGAAGCTTTATCTTCAAGATAACCACATCAATCGGGTGCCCC
CAAATGCTTTTTCTTATCTAAGGCAGCTCTATCGACTGGATATGTCCAATAATAACCTAA
GTAATTTACCTCAGGGTATCTTTGATGATTTGGACAATATAACACAACTGATTCTTCGCA
ACAATCCCTGGTATTGCGGGTGCAAGATGAAATGGGTACGTGACTGGTTACAATCACTAC
CTGTGAAGGTCAACGTGCGTGGGCTCATGTGCCAAGCCCCAGAAAAGGTTCGTGGGATGG
CTATTAAGGATCTCAATGCAGAACTGTTTGATTGTAAGGACAGTGGGATTGTAAGCACCA
TTCAGATAACCACTGCAATACCCAACACAGTGTATCCTGCCCAAGGACAGTGGCCAGCTC
CAGTGACCAAACAGCCAGATATTAAGAACCCCAAGCTCACTAAGGATCAACAAACCACAG
GGAGTCCCTCAAGAAAAACAATTACAATTACTGTGAAGTCTGTCACCTCTGATACCATTC
ATATCTCTTGGAAACTTGCTCTACCTATGACTGCTTTGAGACTCAGCTGGCTTAAACTGG
GCCATAGCCCGGCATTTGGATCTATAACAGAAACAATTGTAACAGGGGAACGCAGTGAGT
ACTTGGTCACAGCCCTGGAGCCTGATTCACCCTATAAAGTATGCATGGTTCCCATGGAAA
CCAGCAACCTCTACCTATTTGATGAAACTCCTGTTTGTATTGAGACTGAAACTGCACCCC
TTCGAATGTACAACCCTACAACCACCCTCAATCGAGAGCAAGAGAAAGAACCTTACAAAA
ACCCCAATTTACCTTTGGCTGCCATCATTGGTGGGGCTGTGGCCCTGGTTACCATTGCCC
TTCTTGCTTTAGTGTGTTGGTATGTTCATAGGAATGGATCGCTCTTCTCAAGGAACTGTG
CATATAGCAAAGGGAGGAGAAGAAAGGATGACTATGCAGAAGCTGGCACTAAGAAGGACA
ACTCTATCCTGGAAATCAGGGAAACTTCTTTTCAGATGTTACCAATAAGCAATGAACCCA
TCTCGAAGGAGGAGTTTGTAATACACACCATATTTCCTCCTAATGGAATGAATCTGTACA
AAAACAATCACAGTGAAAGCAGTAGTAACCGAAGCTACAGAGACAGTGGTATTCCAGACT
CAGATCACTCACACTCATGATGCTGAAGGACTCACAGCAGACTTGTGTTTTGGGTTTTTT
AAACCTAAGGGAGGTGATGGT

FIGURE 274

MISAAWSIFLIGTKIGLFLQVAPLSVMAKSCPSVCRCDAGFIYCNDRFLTSIPTGIPEDA
TTLYLQNNQINNAGIPSDLKNLLKVERIYLYHNSLDEFPTNLPKYVKELHLQENNIRTIT
YDSLSKIPYLEELHLDDNSVSAVSIEEGAFRDSNYLRLLFLSRNHLSTIPWGLPRTIEEL
RLDDNRISTISSPSLQGLTSLKRLVLDGNLLNNHGLGDKVFFNLVNLTELSLVRNSLTAA
PVNLPGTNLRKLYLQDNHINRVPPNAFSYLRQLYRLDMSNNNLSNLPQGIFDDLDNITQL
ILRNNPWYCGCKMKWVRDWLQSLPVKVNVRGLMCQAPEKVRGMAIKDLNAELFDCKDSGI
VSTIQITTAIPNTVYPAQGQWPAPVTKQPDIKNPKLTKDQQTTGSPSRKTITITVKSVTS
DTIHISWKLALPMTALRLSWLKLGHSPAFGSITETIVTGERSEYLVTALEPDSPYKVCMV
PMETSNLYLFDETPVCIETETAPLRMYNPTTTLNREQEKEPYKNPNLPLAAIIGGAVALV
TIALLALVCWYVHRNGSLFSRNCAYSKGRRRKDDYAEAGTKKDNSILEIRETSFQMLPIS
NEPISKEEFVIHTIFPPNGMNLYKNNHSESSSNRSYRDSGIPDSDHSHS

Important features of the protein:
Signal peptide:
amino acids 1-28

Transmembrane domain:
amino acids 531-552

N-glycosylation sites:
amino acids 226-229, 282-285, 296-299, 555-558, 626-629, 633-636

Tyrosine kinase phosphorylation site:
amino acids 515-522

N-myristoylation sites:
amino acids 12-17, 172-177, 208-213, 359-364, 534-539, 556-561, 640-645

Amidation site:
amino acids 567-570

Leucine zipper pattern:
amino acids 159-180

Phospholipase A2 aspartic acid active site:
amino acids 34-44

FIGURE 275

AGGGCCCGCGGGTGGAGAGAGCGACGCCCGAGGGG**ATG**GCGGCAGCGTCCCGGAGCGCCT
CTGGCTGGGCGCTACTGCTGCTGGTGGCACTTTGGCAGCAGCGCGCGGCCGGCTCCGGCG
TCTTCCAGCTGCAGCTGCAGGAGTTCATCAACGAGCGCGGCGTACTGGCCAGTGGGCGGC
CTTGCGAGCCCGGCTGCCGGACTTTCTTCCGCGTCTGCCTTAAGCACTTCCAGGCGGTCG
TCTCGCCCGGACCCTGCACCTTCGGGACCGTCTCCACGCCGGTATTGGGCACCAACTCCT
TCGCTGTCCGGGACGACAGTAGCGGCGGGGGGCGCAACCCTCTCCAACTGCCCTTCAATT
TCACCTGGCCGGGTACCTTCTCGCTCATCATCGAAGCTTGGCACGCGCCAGGAGACGACC
TGCGGCCAGAGGCCTTGCCACCAGATGCACTCATCAGCAAGATCGCCATCCAGGGCTCCC
TAGCTGTGGGTCAGAACTGGTTATTGGATGAGCAAACCAGCACCCTCACAAGGCTGCGCT
ACTCTTACCGGGTCATCTGCAGTGACAACTACTATGGAGACAACTGCTCCCGCCTGTGCA
AGAAGCGCAATGACCACTTCGGCCACTATGTGTGCCAGCCAGATGGCAACTTGTCCTGCC
TGCCCGGTTGGACTGGGGAATATTGCCAACAGCCTATCTGTCTTTCGGGCTGTCATGAAC
AGAATGGCTACTGCAGCAAGCCAGCAGAGTGCCTCTGCCGCCCAGGCTGGCAGGGCCGGC
TGTGTAACGAATGCATCCCCCACAATGGCTGTCGCCACGGCACCTGCAGCACTCCCTGGC
AATGTACTTGTGATGAGGGCTGGGGAGGCCTGTTTTGTGACCAAGATCTCAACTACTGCA
CCCACCACTCCCCATGCAAGAATGGGGCAACGTGCTCCAACAGTGGGCAGCGAAGCTACA
CCTGCACCTGTCGCCCAGGCTACACTGGTGTGGACTGTGAGCTGGAGCTCAGCGAGTGTG
ACAGCAACCCCTGTCGCAATGGAGGCAGCTGTAAGGACCAGGAGGATGGCTACCACTGCC
TGTGTCCTCCGGGCTACTATGGCCTGCACTGTGAACACAGCACCTTGAGCTGCGCCGACT
CCCCCTGCTTCAATGGGGGCTCCTGCCGGGAGCGCAACCAGGGGGCCAACTATGCTTGTG
AATGTCCCCCCAACTTCACCGGCTCCAACTGCGAGAAGAAAGTGGACAGGTGCACCAGCA
ACCCCTGTGCCAACGGGGGACAGTGCCTGAACCGAGGTCCAAGCCGCATGTGCCGCTGCC
GTCCTGGATTCACGGGCACCTACTGTGAACTCCACGTCAGCGACTGTGCCCGTAACCCTT
GCGCCCACGGTGGCACTTGCCATGACCTGGAGAATGGGCTCATGTGCACCTGCCCTGCCG
GCTTCTCTGGCCGACGCTGTGAGGTGCGGACATCCATCGATGCCTGTGCCTCGAGTCCCT
GCTTCAACAGGGCCACCTGCTACACCGACCTCTCCACAGACACCTTTGTGTGCAACTGCC
CTTATGGCTTTGTGGGCAGCCGCTGCGAGTTCCCCGTGGGCTTGCCGCCCAGCTTCCCCT
GGGTGGCCGTCTCGCTGGGTGTGGGGCTGGCAGTGCTGCTGGTACTGCTGGGCATGGTGG
CAGTGGCTGTGCGGCAGCTGCGGCTTCGACGGCCGGACGACGGCAGCAGGGAAGCCATGA
ACAACTTGTCGGACTTCCAGAAGGACAACCTGATTCCTGCCGCCCAGCTTAAAAACACAA
ACCAGAAGAAGGAGCTGGAAGTGGACTGTGGCCTGGACAAGTCCAACTGTGGCAAACAGC
AAAACCACACATTGGACTATAATCTGGCCCCAGGGCCCCTGGGGCGGGGGACCATGCCAG
GAAAGTTTCCCCACAGTGACAAGAGCTTAGGAGAGAAGGCGCCACTGCGGTTACACAGTG
AAAAGCCAGAGTGTCGGATATCAGCGATATGCTCCCCCAGGGACTCCATGTACCAGTCTG
TGTGTTTGATATCAGAGGAGAGGAATGAATGTGTCATTGCCACGGAGGTA**TAA**GGCAGGA
GCCTACCTGGACATCCCTGCTCAGCCCCGCGGCTGGACCTTCCTTCTGCATTGTTTACA

FIGURE 276

MAAASRSASGWALLLLVALWQQRAAGSGVFQLQLQEFINERGVLASGRPCEPGCRTFFRV
CLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSSGGGRNPLQLPFNFTWPGTFSLIIE
AWHAPGDDLRPEALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTRLRYSYRVICSDNYY
GDNCSRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYCSKPAECL
CRPGWQGRLCNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCELELSECDSNPCRNGGSCKDQEDGYHCLCPPGYYGLHCE
HSTLSCADSPCFNGGSCRERNQGANYACECPPNFTGSNCEKKVDRCTSNPCANGGQCLNR
GPSRMCRCRPGFTGTYCELHVSDCARNPCAHGGTCHDLENGLMCTCPAGFSGRRCEVRTS
IDACASSPCFNRATCYTDLSTDTFVCNCPYGFVGSRCEFPVGLPPSFPWVAVSLGVGLAV
LLVLLGMVAVAVRQLRLRRPDDGSREAMNNLSDFQKDNLIPAAQLKNTNQKKELEVDCGL
DKSNCGKQQNHTLDYNLAPGPLGRGTMPGKFPHSDKSLGEKAPLRLHSEKPECRISAICS
PRDSMYQSVCLISEERNECVIATEV

Important features of the protein:
Signal peptide:
amino acids 1-26

Transmembrane domain:
amino acids 530-552

N-glycosylation sites:
amino acids 108-112, 183-187, 205-209, 393-397, 570-574, 610-614

Glycosaminoglycan attachment site:
amino acids 96-100

Tyrosine kinase phosphorylation site:
amino acids 340-347

N-myristoylation sites:
amino acids 42-48, 204-210, 258-264, 277-283, 297-303, 383-389, 415-421, 461-467, 522-528, 535-541, 563-569, 599-605, 625-631

Amidation site:
amino acids 471-475

Aspartic acid and asparagine hydroxylation site:
amino acids 339-351

EGF-like domain cysteine pattern signature:
amino acids 173-185, 206-218, 239-251, 270-282, 310-322, 348-360, 388-400, 426-438, 464-476, 506-518

Calcium-binding EGF-like:
amino acids 224-245, 255-276, 295-316, 333-354, 373-394,

FIGURE 277

GGCAGTGCAGCCGCCTCACAGGTCGGCGGACGGGCCAGGCGGGCGGCCTCCTGAACCGAA
CCGAATCGGCTCCTCGGGCCGTCGTCCTCCCGCCCCTCCTCGCCCGCCGCCGGAGTTTTC
TTTCGGTTTCTTCCAAGATTCCTGGCCTTCCCTCGACGGAGCCGGGCCCAGTGCGGGGGC
GCAGGGCGCGGGAGCTCCACCTCCTCGGCTTTCCCTGCGTCCAGAGGCTGGCATGGCGCG
GGCCGAGTACTGAGCGCACGGTCGGGGCACAGCAGGGCCGGGGGGTGCAGCTGGCTCGCG
CCTCCTCTCCGGCCGCCGTCTCCTCCGGTCCCTGGCGAAAGCCATTGAGACACCAGCTGG
ACGTCACGCGCCGGAGCATGTCTGGGAGTCAGAGCGAGGTGGCTCCATCCCCGCAGAGTC
CGCGGAGCCCCGAG**ATG**GGACGGACTTGCGGCCCGGGTCCCGCGTGCTCCTGCTCCTGC
TTCTGCTCCTGCTGGTGTACCTGACTCAGCCAGGCAATGGCAACGAGGGCAGCGTCACTG
GAAGTTGTTATTGTGGTAAAAGAATTTCTTCCGACTCCCCGCCATCGGTTCAGTTCATGA
ATCGTCTCCGGAAACACCTGAGAGCTTACCATCGGTGTCTATACTACACGAGGTTCCAGC
TCCTTTCCTGGAGCGTGTGTGGGGGCAACAAGGACCCATGGGTTCAGGAATTGATGAGCT
GTCTTGATCTCAAAGAATGTGGACATGCTTACTCGGGGATTGTGGCCCACCAGAAGCATT
TACTTCCTACCAGCCCCCCAATTTCTCAGGCCTCAGAGGGGGCATCTTCAGATATCCACA
CCCCTGCCCAGATGCTCCTGTCCACCTTGCAGTCCACTCAGCGCCCCACCCTCCCAGTAG
GATCACTGTCCTCGGACAAAGAGCTCACTCGTCCCAATGAAACCACCATTCACACTGCGG
GCCACAGTCTGGCAGCTGGGCCTGAGGCTGGGGAGAACCAGAAGCAGCCGGAAAAAAATG
CTGGTCCCACAGCCAGGACATCAGCCACAGTGCCAGTCCTGTGCCTCCTGGCCATCATCT
TCATCCTCACCGCAGCCCTTTCCTATGTGCTGTGCAAGAGGAGGAGGGGGCAGTCACCGC
AGTCCTCTCCAGATCTGCCGGTTCATTATATACCTGTGGCACCTGACTCTAATACC**TGA**G
CCAAGAATGGAAGCTTGTGAGGGTAAACTGTGGCTTATTCTTACAAAAAGTGTAATAAAG
GAGACTGACCCCTGACAACATGGTAGGCACTGTAAAAAAAAAAAAAA

FIGURE 278

MGRDLRPGSRVLLLLLLLLLVYLTQPGNGNEGSVTGSCYCGKRISSDSPPSVQFMNRLRK
HLRAYHRCLYYTRFQLLSWSVCGGNKDPWVQELMSCLDLKECGHAYSGIVAHQKHLLPTS
PPISQASEGASSDIHTPAQMLLSTLQSTQRPTLPVGSLSSDKELTRPNETTIHTAGHSLA
AGPEAGENQKQPEKNAGPTARTSATVPVLCLLAIIFILTAALSYVLCKRRRGQSPQSSPD
LPVHYIPVAPDSNT

Important features of the protein:

Signal peptide:
1-26

Transmembrane domain:
204-223

N-glycosylation site:
168-172

cAMP- and cGMP-dependent protein kinase phosphorylation site:
42-46

N-myristoylation site:
29-35, 32-38, 36-42, 156-162

Amidation site:
40-44

FIGURE 279

CGCGAGGCGCGGGGAGCCTGGGACCAGGAGCGAGAGCCGCCTACCTGCAGCCGCCGCCCA
CGGCACGGCAGCCACC<u>ATG</u>GCGCTCCTGCTGTGCTTCGTGCTCCTGTGCGGAGTAGTGGA
TTTCGCCAGAAGTTTGAGTATCACTACTCCTGAAGAGATGATTGAAAAAGCCAAAGGGGA
AACTGCCTATCTGCCATGCAAATTTACGCTTAGTCCCGAAGACCAGGGACCGCTGGACAT
CGAGTGGCTGATATCACCAGCTGATAATCAGAAGGTGGATCAAGTGATTATTTTATATTC
TGGAGACAAAATTTATGATGACTACTATCCAGATCTGAAAGGCCGAGTACATTTTACGAG
TAATGATCTCAAATCTGGTGATGCATCAATAAATGTAACGAATTTACAACTGTCAGATAT
TGGCACATATCAGTGCAAAGTGAAAAAAGCTCCTGGTGTTGCAAATAAGAAGATTCATCT
GGTAGTTCTTGTTAAGCCTTCAGGTGCGAGATGTTACGTTGATGGATCTGAAGAAATTGG
AAGTGACTTTAAGATAAAATGTGAACCAAAAGAAGGTTCACTTCCATTACAGTATGAGTG
GCAAAAATTGTCTGACTCACAGAAAATGCCCACTTCATGGTTAGCAGAAATGACTTCATC
TGTTATATCTGTAAAAAATGCCTCTTCTGAGTACTCTGGGACATACAGCTGTACAGTCAG
AAACAGAGTGGGCTCTGATCAGTGCCTGTTGCGTCTAAACGTTGTCCCTCCTTCAAATAA
AGCTGGACTAATTGCAGGAGCCATTATAGGAACTTTGCTTGCTCTAGCGCTCATTGGTCT
TATCATCTTTTGCTGTCGTAAAAAGCGCAGAGAAGAAAAATATGAAAAGGAAGTTCATCA
CGATATCAGGGAAGATGTGCCACCTCCAAAGAGCCGTACGTCCACTGCCAGAAGCTACAT
CGGCAGTAATCATTCATCCCTGGGGTCCATGTCTCCTTCCAACATGGAAGGATATTCCAA
GACTCAGTATAACCAAGTACCAAGTGAAGACTTTGAACGCACTCCTCAGAGTCCGACTCT
CCCACCTGCTAAGTTCAAGTACCCTTACAAGACTGATGGAATTACAGTTGTA<u>TAA</u>ATATG
GACTACTGAAGAATCTGAAGTATTGTATTATTTGACTTTATTTTAGGCCTCTAGTAAAGA
CTTAAATGTTTTTTAAAAAAAGCACAAGGCACAGAGATTAGAGCAGCTGTAAGAACACAT
CTACTTTATGCAATGGCATTAGACATGTAAGTCAGATGTCATGTCAAAATTAGTACGAGC
CAAATTCTTTGTTAAAAAACCCTATGTATAGTGACACTGATAGTTAAAAGATGTTTTATT
ATATTTTCAATAACTACCACTAACAAATTTTTAACTTTTCATATGCATATTCTGATATGT
GGTCTTTTAGGAAAAGTATGGTTAATAGTTGATTTTTCAAAGGAAATTTTAAAATTCTTA
CGTTCTGTTTAATGTTTTTGCTATTTAGTTAAATACATTGAAGGGAAATACCCGTTCTTT
TCCCCTTTTATGCACACAACAGAAACACGCGTTGTCATGCCTCAAACTATTTTTTATTTG
CAACTACATGATTTCACACAATTCTCTTAAACAACGACATAAAATAGATTTCCTTGTATA
TAAATAACTTACATACGCTCCATAAAGTAAATTCTCAAAGGTGCTAGAACAAATCGTCCA
CTTCTACAGTGTTCTCGTATCCAACAGAGTTGATGCACAATATATAAATACTCAAGTCCA
ATATTAAAAACTTAGGCACTTGACTAACTTTAATAAAATTTCTCAAACTATATCAATATC
TAAAGTGCATATATTTTTTAAGAAAGATTATTCTCAATAACTTCTATAAAAATAAGTTTG
ATGGTTTGGCCCATCTAACTTCACTACTATTAGTAAGAACTTTTAACTTTTAATGTGTAG
TAAGGTTTATTCTACCTTTTTCTCAACATGACACCAACACAATCAAAAACGAAGTTAGTG
AGGTGCTAACATGTGAGGATTAATCCAGTGATTCCGGTCACAATGCATTCCAGGAGGAGG
TACCCATGTCACTGGAATTGGGCGATATGGTTTATTTTTTCTTCCCTGATTTGGATAACC
AAATGGAACAGGAGGAGGATAGTGATTCTGATGGCCATTCCCTCGATACATTCCTGGCTT
TTTTCTGGGCAAAGGGTGCCACATTGGAAGAGGTGGAAATATAAGTTCTGAAATCTGTAG
GGAAGAGAACACATTAAGTTAATTCAAAGGAAAAAATCATCATCTATGTTCCAGATTTCT
CATTAAAGACAAAGTTACCCACAACACTGAGATCACATCTAAGTGACACTCCTATTGTCA
GGTCTAAATACATTAAAAACCTCATGTGTAATAGGCGTATAATGTATAACAGGTGACCAA
TGTTTTCTGAATGCATAAAGAAATGAATAAACTCAAACACAGTACTTCCTAAACAACTTC
AACCAAAAAAGACCAAAACATGGAACGAATGGAAGCTTGTAAGGACATGCTTGTTTTAGT
CCAGTGGTTTCCACAGCTGGCTAAGCCAGGAGTCACTTGGAGGCTTTTAAATACAAAACA
TTGGAGCTGGAGGCCATTATCCTTAGCAAACTAATGCAGAAACAGAAAATCAACTACCGC
ATGTTCTCACTTATAAGTGGGAGGTAATGATAAGAACTTATGAACACAAAGAAGGAAACA
ATAGACATTGGAGTCTATTTGAGAGGGGAGGGTGGGAGAAGGAAAAGGAGCAGAAAAGAT
AACTATTGAGTACTGCCTTCACACCTGGGTGATGAAATAATATGTACAACAAATCCCTGT
GACACATGTTTACCTATGGAACAAACCTTCATGTGTATCCCTAAACCTAAAATAAAAGTT

FIGURE 280

MALLLCFVLLCGVVDFARSLSITTPEEMIEKAKGETAYLPCKFTLSPEDQGPLDIEWLIS
PADNQKVDQVIILYSGDKIYDDYYPDLKGRVHFTSNDLKSGDASINVTNLQLSDIGTYQC
KVKKAPGVANKKIHLVVLVKPSGARCYVDGSEEIGSDFKIKCEPKEGSLPLQYEWQKLSD
SQKMPTSWLAEMTSSVISVKNASSEYSGTYSCTVRNRVGSDQCLLRLNVVPPSNKAGLIA
GAIIGTLLALALIGLIIFCCRKKRREEKYEKEVHHDIREDVPPPKSRTSTARSYIGSNHS
SLGSMSPSNMEGYSKTQYNQVPSEDFERTPQSPTLPPAKFKYPYKTDGITVV

Signal sequence.
amino acids 1-19

Transmembrane domain:
amino acids 236-257

N-glycosylation sites:
amino acids 106-110, 201-205, 298-302

Tyrosine kinase phosphorylation sites:
amino acids 31-39, 78-85, 262-270

N-myristoylation sites:
amino acids 116-122, 208-214, 219-225, 237-243, 241-247, 245-251, 296-302

Myelin P0 protein:
amino acids 96-125

FIGURE 281

TGCATCAGTGCCCAGGCAAGCCCAGGAGTTGACATTTCTCTGCCCAGCCATGGGCCTCAC
CCTGCTCTTGCTGCTGCTCCTGGGACTAGAAGGTCAGGGCATAGTTGGCAGCCTCCCTGA
GGTGCTGCAGGCACCCGTGGGAAGCTCCATTCTGGTGCAGTGCCACTACAGGCTCCAGGA
TGTCAAAGCTCAGAAGGTGTGGTGCCGGTTCTTGCCGGAGGGGTGCCAGCCCCTGGTGTC
CTCAGCTGTGGATCGCAGAGCTCCAGCGGGCAGGCGTACGTTTCTCACAGACCTGGGTGG
GGGCCTGCTGCAGGTGGAAATGGTTACCCTGCAGGAAGAGGATGCTGGCGAGTATGGCTG
CATGGTGGATGGGGCCAGGGGGCCCCAGATTTTGCACAGAGTCTCTCTGAACATACTGCC
CCCAGAGGAAGAAGAAGAGACCCATAAGATTGGCAGTCTGGCTGAGAACGCATTCTCAGA
CCCTGCAGGCAGTGCCAACCCTTTGGAACCCAGCCAGGATGAGAAGAGCATCCCCTTGAT
CTGGGGTGCTGTGCTCCTGGTAGGTCTGCTGGTGGCAGCGGTGGTGCTGTTTGCTGTGAT
GGCCAAGAGGAAACAAGAATCCCTCCTCAGTGGTCCACCACGTCAGTGACTCTGGACCGG
CTGCTGAATTGCCTTTGGATGTACCACACATTAGGCTTGACTCACCACCTTCATTTGACA
ATACCACCTACACCAGCCTACCTCTTGATTCCCCATCAGGAAAACCTTCACTCCCAGCTC
CATCCTCATTGCCCCCTCTACCTCCTAAGGTCCTGGTCTGCTCCAAGCCTGTGACATATG
CCACAGTAATCTTCCCGGGAGGGAACAAGGGTGGAGGGACCTCGTGTGGGCCAGCCCAGA
ATCCACCTAACAATCAGACTCCATCCAGCTAAGCTGCTCATCACACTTTAAACTCATGAG
GACCATCCCTAGGGGTTCTGTGCATCCATCCAGCCAGCTCATGCCCTAGGATCCTTAGGA
TATCTGAGCAACCAGGGACTTTAAGATCTAATCCAATGTCCTAACTTTACTAGGGAAAGT
GACGCTCAGACATGACTGAGATGTCTTGGGGAAGACCTCCCTGCACCCAACTCCCCCACT
GGTTCTTCTACCATTACACACTGGGCTAAATAAACCCTAATAATGATGTGCAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 282

MGLTLLLLLLLGLEGQGIVGSLPEVLQAPVGSSILVQCHYRLQDVKAQKVWCRFLPEGCQ
PLVSSAVDRRAPAGRRTFLTDLGGGLLQVEMVTLQEEDAGEYGCMVDGARGPQILHRVSL
NILPPEEEEETHKIGSLAENAFSDPAGSANPLEPSQDEKSIPLIWGAVLLVGLLVAAVVL
FAVMAKRKQESLLSGPPRQ

Important features of the protein:
Signal peptide:
amino acids 1-15

Transmembrane domain:
amino acids 161-181

N-myristoylation sites:
amino acids 17-23, 172-178

Amidation site:
amino acids 73-79

FIGURE 283

GTAGCATAGTGTGCAGTTCACTGGACCAAAAGCTTTGGCTGCACCTCTTCTGGAAAGCTG
GCC<u>ATG</u>GGGCTCTTCATGATCATTGCAATTCTGCTGTTCCAGAAACCCACAGTAACCGAA
CAACTTAAGAAGTGCTGGAATAACTATGTACAAGGACATTGCAGGAAAATCTGCAGAGTA
AATGAAGTGCCTGAGGCACTATGTGAAAATGGGAGATACTGTTGCCTCAATATCAAGGAA
CTGGAAGCATGTAAAAAAATTACAAAGCCACCTCGTCCAAAGCCAGCAACACTTGCACTG
ACTCTTCAAGACTATGTTACAATAATAGAAAATTTCCCAAGCCTGAAGACACAGTCTACA
<u>TAA</u>ATCAAATACAATTTCGTTTTCACTTGCTTCTCAACCTAGTCTAATAAACTAAGGTGA
TGAGATATACATCTTCTTCCTTCTGGTTTCTTGATCCTTAAAATGACCTTCGAGCATATT
CTAATAAAGTGCATTGCCAGTTAAAAAAAAAAA

FIGURE 284

MGLFMIIAILLFQKPTVTEQLKKCWNNYVQGHCRKICRVNEVPEALCENGRYCCLNIKEL
EACKKITKPPRPKPATLALTLQDYVTIIENFPSLKTQST

Important features of the protein:

Signal peptide:
None

Transmembrane domain:
None

cAMP- and cGMP-dependent protein kinase phosphorylation site:
64-68

FIGURE 285

GATGGCGCAGCCACAGCTTCTGTGAGATTCGATTTCTCCCCAGTTCCCCTGTGGGTCTGA
GGGGACCAGAAGGGTGAGCTACGTTGGCTTTCTGGAAGGGGAGGCTATATGCGTCAATTC
CCCAAAACAAGTTTTGACATTTCCCCTGAAATGTCATTCTCTATCTATTCACTGCAAGTG
CCTGCTGTTCCAGGCCTTACCTGCTGGGCACTAACGGCGGAGCCAGGATGGGGACAGAAT
AAAGGAGCCACGACCTGTGCCACCAACTCGCACTCAGACTCTGAACTCAGACCTGAAATC
TTCTCTTCACGGGAGGCTTGGCAGTTTTTCTTACTCCTGTGGTCTCCAGATTTCAGGCCT
AAG**ATG**AAAGCCTCTAGTCTTGCCTTCAGCCTTCTCTCTGCTGCGTTTTATCTCCTATGG
ACTCCTTCCACTGGACTGAAGACACTCAATTTGGGAAGCTGTGTGATCGCCACAAACCTT
CAGGAAATACGAAATGGATTTTCTGAGATACGGGGCAGTGTGCAAGCCAAAGATGGAAAC
ATTGACATCAGAATCTTAAGGAGGACTGAGTCTTTGCAAGACACAAAGCCTGCGAATCGA
TGCTGCCTCCTGCGCCATTTGCTAAGACTCTATCTGGACAGGGTATTTAAAAACTACCAG
ACCCCTGACCATTATACTCTCCGGAAGATCAGCAGCCTCGCCAATTCCTTTCTTACCATC
AAGAAGGACCTCCGGCTCTCTCATGCCCACATGACATGCCATTGTGGGGAGGAAGCAATG
AAGAAATACAGCCAGATTCTGAGTCACTTTGAAAAGCTGGAACCTCAGGCAGCAGTTGTG
AAGGCTTTGGGGGAACTAGACATTCTTCTGCAATGGATGGAGGAGACAGAA**TAG**GAGGAA
AGTGATGCTGCTGCTAAGAATATTCGAGGTCAAGAGCTCCAGTCTTCAATACCTGCAGAG
GAGGCATGACCCCAAACCACCATCTCTTTACTGTACTAGTCTTGTGCTGGTCACAGTGTA
TCTTATTTATGCATTACTTGCTTCCTTGCATGATTGTCTTTATGCATCCCCAATCTTAAT
TGAGACCATACTTGTATAAGATTTTTGTAATATCTTTCTGCTATTGGATATATTTATTAG
TTAATATATTTATTTATTTTTTGCTATTTAATGTATTTATTTTTTTACTTGGACATGAAA
CTTTAAAAAAATTCACAGATTATATTTATAACCTGACTAGAGCAGGTGATGTATTTTTAT
ACAGTAAAAAAAAAAAAACCTTGTAAATTCTAGAAGAGTGGCTAGGGGGGTTATTCATTTG
TATTCAACTAAGGACATATTTACTCATGCTGATGCTCTGTGAGATATTTGAAATTGAACC
AATGACTACTTAGGATGGGTTGTGGAATAAGTTTTGATGTGGAATTGCACATCTACCTTA
CAATTACTGACCATCCCCAGTAGACTCCCCAGTCCCATAATTGTGTATCTTCCAGCCAGG
AATCCTACACGGCCAGCATGTATTTCTACAAATAAAGTTTTCTTTGCATACCAAAAAAAA
AAAAAAAAAAA

FIGURE 286

MKASSLAFSLLSAAFYLLWTPSTGLKTLNLGSCVIATNLQEIRNGFSEIRGSVQAKDGNI
DIRILRRTESLQDTKPANRCCLLRHLLRLYLDRVFKNYQTPDHYTLRKISSLANSFLTIK
KDLRLSHAHMTCHCGEEAMKKYSQILSHFEKLEPQAAVVKALGELDILLQWMEETE

FIGURE 287

AATGCCCC**ATG**CGCACCCCACAGCTCGCGCTCCTGCAAGTGTTCTTTCTGGTGTTCCCCG
ATGGCGTCCGGCCTCAGCCCTCTTCCTCCCCATCAGGGGCAGTGCCCACGTCTTTGGAGC
TGCAGCGAGGGACGGATGGCGGAACCCTCCAGTCCCCTTCAGAGGCGACTGCAACTCGCC
CGGCCGTGCCTGGACTCCCTACAGTGGTCCCTACTCTCGTGACTCCCTCGGCCCCTGGGA
ATAGGACTGTGGACCTCTTCCCAGTCTTACCGATCTGTGTCTGTGACTTGACTCCTGGAG
CCTGCGATATAAATTGCTGCTGCGACAGGGACTGCTATCTTCTCCATCCGAGGACAGTTT
TCTCCTTCTGCCTTCCAGGCAGCGTAAGGTCTTCAAGCTGGGTTTGTGTAGACAACTCTG
TTATCTTCAGGAGTAATTCCCCGTTTCCTTCAAGAGTTTTCATGGATTCTAATGGAATCA
GGCAGTTTTGTGTCCATGTGAACAACTCAAACTTAAACTATTTCCAGAAGCTTCAAAAGG
TCAATGCAACCAACTTCCAGGCCCTGGCTGCAGAGTTTGGAGGCGAATCATTCACTTCAA
CATTCCAAACTCAATCACCACCATCTTTTTACAGGGCTGGGGACCCCATTCTTACTTACT
TCCCCAAGTGGTCTGTAATAAGCTTGCTGAGACAACCTGCAGGAGTTGGAGCTGGGGGAC
TCTGTGCTGAAAGCAATCCTGCAGGTTTCCTAGAGAGTAAAAGTACAACTTGCACTCGTT
TTTTCAAGAACCTGGCTAGTAGCTGTACCTTGGATTCAGCCCTCAATGCTGCCTCTTACT
ATAACTTCACAGTCTTAAAGGTTCCAAGAAGCATGACTGATCCACAGAATATGGAGTTCC
AGGTTCCTGTAATACTTACCTCACAGGCTAATGCTCCTCTGTTGGCTGGAAACACTTGTC
AGAATGTAGTTTCTCAGGTCACCTATGAGATAGAGACCAATGGGACTTTTGGAATCCAGA
AAGTTTCTGTCAGTTTGGGACAAACCAACCTGACTGTTGAGCCAGGCGCTTCCTTACAGC
AACACTTCATCCTTCGCTTCAGGGCTTTTCAACAGAGCACAGCTGCTTCTCTCACCAGTC
CTAGAAGTGGGAATCCTGGCTATATAGTTGGGAAGCCACTCTTGGCTCTGACTGATGATA
TAAGTTACTCAATGACCCTCTTACAGAGCCAGGGTAATGGAAGTTGCTCTGTTAAAAGAC
ATGAAGTGCAGTTTGGAGTGAATGCAATATCTGGATGCAAGCTCAGGTTGAAGAAGGCAG
ACTGCAGCCACTTGCAGCAGGAGATTTATCAGACTCTTCATGGAAGGCCCAGACCAGAGT
ATGTTGCCATCTTTGGTAATGCTGACCCAGCCCAGAAAGGAGGGTGGACCAGGATCCTCA
ACAGGCACTGCAGCATTTCAGCTATAAACTGTACTTCCTGCTGTCTCATACCAGTTTCCC
TGGAGATCCAGGTATTGTGGGCATATGTAGGTCTCCTGTCCAACCCGCAAGCTCATGTAT
CAGGAGTTCGATTCCTATACCAGTGCCAGTCTATACAGGATTCTCAGCAAGTTACAGAAG
TATCTTTGACAACTCTTGTGAACTTTGTGGACATTACCCAGAAGCCACAGCCTCCAAGGG
GCCAACCCAAAATGGACTGGAAATGGCCATTCGACTTCTTTCCCTTCAAAGTGGCATTCA
GCAGAGGAGTATTCTCTCAAAAATGCTCAGTCTCTCCCATCCTTATCCTGTGCCTCTTAC
TACTTGGAGTTCTCAACCTAGAGACTATG**TGA**AGAAAAGAAAATAATCAGATTTCAGTTT
TCCCTATGAGAAACTCTGAGGCAGCCACTTATCTTGGCTAAATAGAACCTCACCTGCTCA
TGACCAGAGAGCATTTAGGATAATAGATGACCTAACTGAAGGAATCCTTGTATATGAAAG
GAGTTATTTTAGAAAAGCAATAAAAATATTTTATTCATCNTAAAAAAAAAA

FIGURE 288

MRTPQLALLQVFFLVFPDGVRPQPSSSPSGAVPTSLELQRGTDGGTLQSPSEATATRPAV
PGLPTVVPTLVTPSAPGNRTVDLFPVLPICVCDLTPGACDINCCCDRDCYLLHPRTVFSF
CLPGSVRSSSWVCVDNSVIFRSNSPFPSRVFMDSNGIRQFCVHVNNSNLNYFQKLQKVNA
TNFQALAAEFGGESFTSTFQTQSPPSFYRAGDPILTYFPKWSVISLLRQPAGVGAGGLCA
ESNPAGFLESKSTTCTRFFKNLASSCTLDSALNAASYYNFTVLKVPRSMTDPQNMEFQVP
VILTSQANAPLLAGNTCQNVVSQVTYEIETNGTFGIQKVSVSLGQTNLTVEPGASLQQHF
ILRFRAFQQSTAASLTSPRSGNPGYIVGKPLLALTDDISYSMTLLQSQGNGSCSVKRHEV
QFGVNAISGCKLRLKKADCSHLQQEIYQTLHGRPRPEYVAIFGNADPAQKGGWTRILNRH
CSISAINCTSCCLIPVSLEIQVLWAYVGLLSNPQAHVSGVRFLYQCQSIQDSQQVTEVSL
TTLVNFVDITQKPQPPRGQPKMDWKWPFDFFPFKVAFSRGVFSQKCSVSPILILCLLLLG
VLNLETM

Important features of the protein:
Signal peptide:
amino acids 1-22

Transmembrane domains:
amino acids 484-505, 581-600

N-glycosylation sites:
amino acids 78-82, 165-169, 179-185, 279-285, 331-337, 347-351, 410-414, 487-491

N-myristoylation sites:
amino acids 30-36, 41-47, 124-130, 232-238, 236-242, 409-415

Prokaryotic membrane lipoprotein lipid attachment site:
amino acids 420-431

FIGURE 289

CGCGGAGCCCTGCGCTGGGAGGTGCACGGTGTGCACGCTGGACTGGACCCCCATGCAACC
CCGCGCCCTGCGCCTTAACCAGGACTGCTCCGCGCGCCCCTGAGCCTCGGGCTCCGGCCC
GGACCTGCAGCCTCCCAGGTGGCTGGGAAGAACTCTCCAACAATAAATACATTTGATAAG
AAAG<u>ATG</u>GCTTTAAAAGTGCTACTAGAACAAGAGAAAACGTTTTTCACTCTTTTAGTATT
ACTAGGCTATTTGTCATGTAAAGTGACTTGTGAATCAGGAGACTGTAGACAGCAAGAATT
CAGGGATCGGTCTGGAAACTGTGTTCCCTGCAACCAGTGTGGGCCAGGCATGGAGTTGTC
TAAGGAATGTGGCTTCGGCTATGGGGAGGATGCACAGTGTGTGACGTGCCGGCTGCACAG
GTTCAAGGAGGACTGGGGCTTCCAGAAATGCAAGCCCTGTCTGGACTGCGCAGTGGTGAA
CCGCTTTCAGAAGGCAAATTGTTCAGCCACCAGTGATGCCATCTGCGGGGACTGCTTGCC
AGGATTTTATAGGAAGACGAAACTTGTCGGCTTTCAAGACATGGAGTGTGTGCCTTGTGG
AGACCCTCCTCCTCCTTACGAACCGCACTGTGCCAGCAAGGTCAACCTCGTGAAGATCGC
GTCCACGGCCTCCAGCCCACGGGACACGGCGCTGGCTGCCGTTATCTGCAGCGCTCTGGC
CACCGTCCTGCTGGCCCTGCTCATCCTCTGTGTCATCTATTGTAAGAGACAGTTTATGGA
GAAGAAACCCAGCTGGTCTCTGCGGTCGCAGGACATTCAGTACAACGGCTCTGAGCTGTC
GTGTTTTGACAGACCTCAGCTCCACGAATATGCCCACAGAGCCTGCTGCCAGTGCCGCCG
TGACTCAGTGCAGACCTGCGGGCCGGTGCGCTTGCTCCCATCCATGTGCTGTGAGGAGGC
CTGCAGCCCCAACCCGGCGACTCTTGGTTGTGGGGTGCATTCTGCAGCCAGTCTTCAGGC
AAGAAACGCAGGCCCAGCCGGGGAGATGGTGCCGACTTTCTTCGGATCCCTCACGCAGTC
CATCTGTGGCGAGTTTTCAGATGCCTGGCCTCTGATGCAGAATCCCATGGGTGGTGACAA
CATCTCTTTTTGTGACTCTTATCCTGAACTCACTGGAGAAGACATTCATTCTCTCAATCC
AGAACTTGAAAGCTCAACGTCTTTGGATTCAAATAGCAGTCAAGATTTGGTTGGTGGGGC
TGTTCCAGTCCAGTCTCATTCTGAAAACTTTACAGCAGCTACTGATTTATCTAGATATAA
CAACACACTGGTAGAATCAGCATCAACTCAGGATGCACTAACTATGAGAAGCCAGCTAGA
TCAGGAGAGTGGCGCTGTCATCCACCCAGCCACTCAGACGTCCCTCCAGGAAGCT<u>**TAA**</u>AG
AACCTGCTTCTTTCTGCAGTAGAAGCGTGTGCTGGAACCCAAAGAGTACTCCTTTGTTAG
GCTTATGGACTGAGCAGTCTGGACCTTGCATGGCTTCTGGGGCAAAAATAAATCTGAACC
AAACTGACGGCATTTGAAGCCTTTCAGCCAGTTGCTTCTGAGCCAGACCAGCTGTAAGCT
GAAACCTCAATGAATAACAAGAAAAGACTCCAGGCCGACTCATGATACTCTGCATCTTTC
CTACATGAGAAGCTTCTCTGCCACAAAAGTGACTTCAAAGACTGATGGGTTGAGCTGGCA
GCCTATGAGATTGTGGACATATAACAAGAAACAGAAATGCCCTCATGCTTATTTTCATGG
TGATTGTGGTTTTACAAGACTGAAGACCCAGAGTATACTTTTTCTTTCCAGAAATAATTT
CATACCGCCTATGAAATATCAGATAAATTACCTTAGCTTTTATGTAGAATGGGTTCAAAA
GTGAGTGTTTCTATTTGAGAAGGACACTTTTTCATCATCTAAACTGATTCGCATAGGTGG
TTAGAATGGCCCTCATATTGCCTGCCTAAATCTTGGGTTTATTAGATGAAGTTTACTGAA
TCAGAGGAATCAGACAGAGGAGGATAGCTCTTTCCAGAATCCACACTTCTGACCTCAGCC
TCGGTCTCATGAACACCCGCTGATCTCAGGAGAACACCTGGGCTAGGGAATGTGGTCGAG
AAAGGGCAGCCCATTGCCCAGAATTAACACATATTGTAGAGACTTGTATGCAAAGGTTGG
CATATTTATATGAAAATTAGTTGCTATAGAAACATTTGTTGCATCTGTCCCTCTGCCTGA
GCTTAGAAGGTTATAGAAAAAGGGTATTTATAAACATAAATGACCTTTTACTTGCATTGT
ATCTTATACTAAAGGCTTTAGAAATTACAACATATCAGGTTCCCCTACTACTGAAGTAGC
CTTCCGTGAGAACACACCACATGTTAGGACTAGAAGAAAATGCACAATTTGTAGGGGTTT
GGATGAAGCAGCTGTAACTGCCCTAGTGTAGTTTGACCAGGACATTGTCGTGCTCCTTCC
AATTGTGTAAGATTAGTTAGCACATCATCTCCTACTTTAGCCATCCGGTGTTGGATTTAA
GAGGACGGTGCTTCTTTCTATTAAAGTGCTCCATCCCCTACCATCTACACATTAGCATTG
TCTCTAGAGCTAAGACAGAAATTAACCCCGTTCAGTCACAAAGCAGGGAATGGTTCATTT
ACTCTTAATCTTTATGCCCTGGAGAAGACCTACTTGAACAGGGCATATTTTTTAGACTTC
TGAACATCAGTATGTTCGAGGGTACTATGATATTTTGGTTTGGAATTGCCCTGCCCAAGT
CACTGTCTTTTAACTTTTAAACTGAATATTAAAATGTATCTGTCTTTCCT

FIGURE 290

MALKVLLEQEKTFFTLLVLLGYLSCKVTCESGDCRQQEFRDRSGNCVPCNQCGPGMELSK
ECGFGYGEDAQCVTCRLHRFKEDWGFQKCKPCLDCAVVNRFQKANCSATSDAICGDCLPG
FYRKTKLVGFQDMECVPCGDPPPPYEPHCASKVNLVKIASTASSPRDTALAAVICSALAT
VLLALLILCVIYCKRQFMEKKPSWSLRSQDIQYNGSELSCFDRPQLHEYAHRACCQCRRD
SVQTCGPVRLLPSMCCEEACSPNPATLGCGVHSAASLQARNAGPAGEMVPTFFGSLTQSI
CGEFSDAWPLMQNPMGGDNISFCDSYPELTGEDIHSLNPELESSTSLDSNSSQDLVGGAV
PVQSHSENFTAATDLSRYNNTLVESASTQDALTMRSQLDQESGAVIHPATQTSLQEA

Important features of the protein:
Signal peptide:
Amino acids 1-25

Transmembrane domain:
Amino acids 169-192

N-glycosylation sites:
Amino acids 105-109;214-218;319-323;350-354;368-372;379-383

cAMP- and cGMP-dependent protein kinase phosphorylation sites:
Amino acids 200-204;238-242

Tyrosine kinase phosphorylation site:
Amino acids 207-214

N-myristoylation sites:
Amino acids 55-61;215-221;270-276

Prokaryotic membrane lipoprotein lipid attachment site:
Amino acids 259-270

TNFR/NGFR family cysteine-rich region proteins:
Amino acids 89-96

FIGURE 291

CCTGGAGCCGGAAGCGCGGCTGCAGCAGGGCGAGGCTCCAGGTGGGGTCGGTTCCGCATC
CAGCCTAGCGTGTCCACG**ATG**CGGCTGGGCTCCGGGACTTTCGCTACCTGTTGCGTAGCG
ATCGAGGTGCTAGGGATCGCGGTCTTCCTTCGGGGATTCTTCCCGGCTCCCGTTCGTTCC
TCTGCCAGAGCGGAACACGGAGCGGAGCCCCCAGCGCCCGAACCCTCGGCTGGAGCCAGT
TCTAACTGGACCACGCTGCCACCACCTCTCTTCAGTAAAGTTGTTATTGTTCTGATAGAT
GCCTTGAGAGATGATTTTGTGTTTGGGTCAAAGGGTGTGAAATTTATGCCCTACACAACT
TACCTTGTGGAAAAAGGAGCATCTCACAGTTTTGTGGCTGAAGCAAAGCCACCTACAGTT
ACTATGCCTCGAATCAAGGCATTGATGACGGGGAGCCTTCCTGGCTTTGTCGACGTCATC
AGGAACCTCAATTCTCCTGCACTGCTGGAAGACAGTGTGATAAGACAAGCAAAAGCAGCT
GGAAAAAGAATAGTCTTTTATGGAGATGAAACCTGGGTTAAATTATTCCCAAAGCATTTT
GTGGAATATGATGGAACAACCTCATTTTTCGTGTCAGATTACACAGAGGTGGATAATAAT
GTCACGAGGCATTTGGATAAAGTATTAAAAAGAGGAGATTGGGACATATTAATCCTCCAC
TACCTGGGGCTGGACCACATTGGCCACATTTCAGGGCCCAACAGCCCCCTGATTGGGCAG
AAGCTGAGCGAGATGGACAGCGTGCTGATGAAGATCCACACCTCACTGCAGTCGAAGGAG
AGAGAGACGCCTTTACCCAATTTGCTGGTTCTTTGTGGTGACCATGGCATGTCTGAAACA
GGAAGTCACGGGGCCTCCTCCACCGAGGAGGTGAATACACCTCTGATTTTAATCAGTTCT
GCGTTTGAAAGGAAACCCGGTGATATCCGACATCCAAAGCACGTCCAA**TAG**ACGGATGTG
GCTGCGACACTGGCGATAGCACTTGGCTTACCGATTCCAAAAGACAGTGTAGGGAGCCTC
CTATTCCCAGTTGTGGAAGGAAGACCAATGAGAGAGCAGTTGAGATTTTTACATTTGAAT
ACAGTGCAGCTTAGTAAACTGTTGCAAGAGAATGTGCCGTCATATGAAAAAGATCCTGGG
TTTGAGCAGTTTAAAATGTCAGAAAGATTGCATGGGAACTGGATCAGACTGTACTTGGAG
GAAAAGCATTCAGAAGTCCTATTCAACCTGGGCTCCAAGGTTCTCAGGCAGTACCTGGAT
GCTCTGAAGACGCTGAGCTTGTCCCTGAGTGCACAAGTGGCCCAGTTCTCACCCTGCTCC
TGCTCAGCGTCCCACAGGCACTGCACAGAAAGGCTGAGCTGGAAGTCCCACTGTCATCTC
CTGGGTTTTCTCTGCTCTTTTATTTGGTGATCCTGGTTCTTTCGGCCGTTCACGTCATTG
TGTGCACCTCAGCTGAAAGTTCGTGCTACTTCTGTGGCCTCTCGTGGCTGGCGGCAGGCT
GCCTTTCGTTTACCAGACTCTGGTTGAACACCTGGTGTGTGCCAAGTGCTGGCAGTGCCC
TGGACAGGGGGCCTCAGGGAAGGACGTGGAGCAGCCTTATCCCAGGCCTCTGGGTGTCCC
GACACAGGTGTTCACATCTGTGCTGTCAGGTCAGATGCCTCAGTTCTTGGAAAGCTAGGT
TCCTGCGACTGTTACCAAGGTGATTGTAAAGAGCTGGCGGTCACAGAGGAACAAGCCCCC
CAGCTGAGGGGGTGTGTGAATCGGACAGCCTCCCAGCAGAGGTGTGGGAGCTGCAGCTGA
GGGAAGAAGAGACAATCGGCCTGGACACTCAGGAGGGTCAAAAGGAGACTTGGTCGCACC
ACTCATCCTGCCACCCCCAGAATGCATCCTGCCTCATCAGGTCCAGATTTCTTTCCAAGG
CGGACGTTTTCTGTTGGAATTCTTAGTCCTTGGCCTCGGACACCTTCATTCGTTAGCTGG
GGAGTGGTGGTGAGGCAGTGAAGAAGAGGCGGATGGTCACACTCAGATCCACAGAGCCCA
GGATCAAGGGACCCACTGCAGTGGCAGCAGGACTGTTGGGCCCCCACCCCAACCCTGCAC
AGCCCTCATCCCCTCTTGGCTTGAGCCGTCAGAGGCCCTGTGCTGAGTGTCTGACCGAGA
CACTCACAGCTTTGTCATCAGGGCACAGGCTTCCTCGGAGCCAGGATGATCTGTGCCACG
CTTGCACCTCGGGCCCATCTGGGCTCATGCTCTCTCTCCTGCTATTGAATTAGTACCTAG
CTGCACACAGTATGTAGTTACCAAAAGAATAAACGGCAATAATTGAGAAAAAAAA

FIGURE 292

MRLGSGTFATCCVAIEVLGIAVFLRGFFPAPVRSSARAEHGAEPPAPEPSAGASSNWTTL
PPPLFSKVVIVLIDALRDDFVFGSKGVKFMPYTTYLVEKGASHSFVAEAKPPTVTMPRIK
ALMTGSLPGFVDVIRNLNSPALLEDSVIRQAKAAGKRIVFYGDETWVKLFPKHFVEYDGT
TSFFVSDYTEVDNNVTRHLDKVLKRGDWDILILHYLGLDHIGHISGPNSPLIGQKLSEMD
SVLMKIHTSLQSKERETPLPNLLVLCGDHGMSETGSHGASSTEEVNTPLILISSAFERKP
GDIRHPKHVQ

Important features of the protein:
Signal peptide:
amino acids 1-34

Transmembrane domain:
amino acids 58-76

N-glycosylation sites:
amino acids 56-60, 194-198

N-myristoylation sites:
amino acids 6-12, 52-58, 100-106, 125-131, 233-239, 270-276, 275-281, 278-284

Amidation site:
amino acids 154-158

Cell attachment sequence:
amino acids 205-208

FIGURE 293

AGCCAGGCAGCACATCACAGCGGGAGGAGCTGTCCCAGGTGGCCCAGCTCAGCA**ATG**GCA
ATGGGGGTCCCCAGAGTCATTCTGCTCTGCCTCTTTGGGGCTGCGCTCTGCCTGACAGGG
TCCCAAGCCCTGCAGTGCTACAGCTTTGAGCACACCTACTTTGGCCCCTTTGACCTCAGG
GCCATGAAGCTGCCCAGCATCTCCTGTCCTCATGAGTGCTTTGAGGCTATCCTGTCTCTG
GACACCGGGTATCGCGCGCCGGTGACCCTGGTGCGGAAGGGCTGCTGGACCGGGCCTCCT
GCGGGCCAGACGCAATCGAACCCGGACGCGCTGCCGCCAGACTACTCGGTGGTGCGCGGC
TGCACAACTGACAAATGCAACGCCCACCTCATGACTCATGACGCCCTCCCCAACCTGAGC
CAAGCACCCGACCCGCCGACGCTCAGCGGCGCCGAGTGCTACGCCTGTATCGGGGTCCAC
CAGGATGACTGCGCTATCGGCAGGTCCCGACGAGTCCAGTGTCACCAGGACCAGACCGCC
TGCTTCCAGGGCAGTGGCAGAATGACAGTTGGCAATTTCTCAGTCCCTGTGTACATCAGA
ACCTGCCACCGGCCCTCCTGCACCACCGAGGGCACCACCAGCCCCTGGACAGCCATCGAC
CTCCAGGGCTCCTGCTGTGAGGGGTACCTCTGCAACAGGAAATCCATGACCCAGCCCTTC
ACCAGTGCTTCAGCCACCACCCCTCCCCGAGCACTACAGGTCCTGGCCCTGCTCCTCCCA
GTCCTCCTGCTGGTGGGGCTCTCAGCA**TAG**ACCGCCCCTCCAGGATGCTGGGGACAGGGC
TCACACACCTCATTCTTGCTGCTTCAGCCCCTATCACATAGCTCACTGGAAAATGATGTT
AAAGTAAGAATTGCAAAA

FIGURE 294

MAMGVPRVILLCLFGAALCLTGSQALQCYSFEHTYFGPFDLRAMKLPSISCPHECFEAIL
SLDTGYRAPVTLVRKGCWTGPPAGQTQSNPDALPPDYSVVRGCTTDKCNAHLMTHDALPN
LSQAPDPPTLSGAECYACIGVHQDDCAIGRSRRVQCHQDQTACFQGSGRMTVGNFSVPVY
IRTCHRPSCTTEGTTSPWTAIDLQGSCCEGYLCNRKSMTQPFTSASATTPPRALQVLALL
LPVLLLVGLSA

Important features of the protein:
Signal peptide:
amino acids 1-19

Transmembrane domain:
amino acids 233-251

N-glycosylation sites:
amino acids 120-124, 174-178

N-myristoylation sites:
amino acids 15-21, 84-90

FIGURE 295

AATCGGCTGATTCTGCATCTGGAAACTGCCTTCATCTTGAAAGAAAAGCTCCAGGTCCCT
TCTCCAGCCACCCAGCCCCAAG<u>ATG</u>GTGATGCTGCTGCTGCTGCTTTCCGCACTGGCTGG
CCTCTTCGGTGCGGCAGAGGGACAAGCATTTCATCTTGGGAAGTGCCCCAATCCTCCGGT
GCAGGAGAATTTTGACGTGAATAAGTATCTCGGAAGATGGTACGAAATTGAGAAGATCCC
AACAACCTTTGAGAATGGACGCTGCATCCAGGCCAACTACTCACTAATGGAAAACGGAAA
GATCAAAGTGTTAAACCAGGAGTTGAGAGCTGATGGAACTGTGAATCAAATCGAAGGTGA
AGCCACCCCAGTTAACCTCACAGAGCCTGCCAAGCTGGAAGTTAAGTTTTCCTGGTTTAT
GCCATCGGCACCGTACTGGATCCTGGCCACCGACTATGAGAACTATGCCCTCGTGTATTC
CTGTACCTGCATCATCCAACTTTTTCACGTGGATTTTGCTTGGATCTTGGCAAGAAACCC
TAATCTCCCTCCAGAAACAGTGGACTCTCTAAAAAATATCCTGACTTCTAATAACATTGA
TGTCAAGAAAATGACGGTCACAGACCAGGTGAACTGCCCCAAGCTCTCG<u>TAA</u>CCAGGTTC
TACAGGGAGGCTGCACCCACTCCATGTTACTTCTGCTTCGCTTTCCCCTACCCCACCCCC
CCCCCATAAAGACAAACCAATCAACCACGACAAAGGAAGTTGACCTGAACATGTAACCAT
GCCCTACCCTGTTACCTTGCTAGCTGCAAAATAAACTTGTTGCTGACCTGCTGTGCTCGC
AAAAAA

FIGURE 296

MVMLLLLLSALAGLFGAAEGQAFHLGKCPNPPVQENFDVNKYLGRWYEIEKIPTTFENG
RCIQANYSLMENGKIKVLNQELRADGTVNQIEGEATPVNLTEPAKLEVKFSWFMPSAPY
WILATDYENYALVYSCTCIIQLFHVDFAWILARNPNLPPETVDSLKNILTSNNIDVKKM
TVTDQVNCPKLS

Signal sequence:
1-16

N-glycosylation site:
65-68
98-101

cAMP- and cGMP-dependent protein kinase phosphorylation site:
175-178

N-myristoylation site:
13-18
16-21

Lipocalin proteins:
36-47
120-130

Lipocalin / cytosolic fatty-acid binding proteins:
41-185

FIGURE 297

GGGTGATTGAACTAAACCTTCGCCGCACCGAGTTTGCAGTACGGCCGTCACCCGCACCGC
TGCCTGCTTGCGGTTGGAGAAATCAAGGCCCTACCGGGCCTCCGTAGTCACCTCTCTATA
GTGGGCGTGGCCGAGGCCGGGGTGACCCTGCCGGAGCCTCCGCTGCCAGCGAC**ATG**TTCA
AGGTAATTCAGAGGTCCGTGGGGCCAGCCAGCCTGAGCTTGCTCACCTTCAAAGTCTATG
CAGCACCAAAAAAGGACTCACCTCCCAAAAATTCCGTGAAGGTTGATGAGCTTTCACTCT
ACTCAGTTCCTGAGGGTCAATCGAAGTATGTGGAGGAGGCAAGGAGCCAGCTTGAAGAAA
GCATCTCACAGCTCCGACACTATTGCGAGCCATACACAACCTGGTGTCAGGAAACGTACT
CCCAAACTAAGCCCAAGATGCAAAGTTTGGTTCAATGGGGGTTAGACAGCTATGACTATC
TCCAAAATGCACCTCCTGGATTTTTTCCGAGACTTGGTGTTATTGGTTTTGCTGGCCTTA
TTGGACTCCTTTTGGCTAGAGGTTCAAAAATAAAGAAGCTAGTGTATCCGCCTGGTTTCA
TGGGATTAGCTGCCTCCCTCTATTATCCACAACAAGCCATCGTGTTTGCCCAGGTCAGTG
GGGAGAGATTATATGACTGGGGTTTACGAGGATATATAGTCATAGAAGATTTGTGGAAGG
AGAACTTTCAAAAGCCAGGAAATGTGAAGAATTCACCTGGAACTAAG**TAG**AAAACTCCAT
GCTCTGCCATCTTAATCAGTTATAGGTAAACATTGGAAACTCCATAGAATAAATCAGTAT
TTCTACAGAAAAATGGCATAGAAGTCAGTATTGAATGTATTAAATTGGCTTTCTTCTTCA
GGAAAAACTAGACCAGACCTCTGTTATCTTCTGTGAAATCATCCTACAAGCAAACTAACC
TGGAATCCCTTCACCTAGAGATAATGTACAAGCCTTAGAACTCCTCATTCTCATGTTGCT
ATTTATGTACCTAATTAAAACCCAAGTTTAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAA

FIGURE 298

MFKVIQRSVGPASLSLLTFKVYAAPKKDSPPKNSVKVDELSLYSVPEGQSKYVEEARSQL
EESISQLRHYCEPYTTWCQETYSQTKPKMQSLVQWGLDSYDYLQNAPPGFFPRLGVIGFA
GLIGLLLARGSKIKKLVYPPGFMGLAASLYYPQQAIVFAQVSGERLYDWGLRGYIVIEDL
WKENFQKPGNVKNSPGTK

Important features:
Signal peptide:
Amino acids 1-23

Transmembrane domain:
Amino acids 111-130

cAMP- and cGMP-dependent protein kinase phosphorylation site:
Amino acids 26-30

Tyrosine kinase phosphorylation site:
Amino acids 36-44

N-myristoylation sites:
Amino acids 124-130;144-150;189-195

FIGURE 299

CCGCTGAGATGTACGAACTTCCGGTTCTCCGGGCAGCTGCCACTGCTGTAGCTTCTGCCA
CCTGCCACGACCGGGCCTCTCCCTGGCGTTTGGTCACCTCTGCTTCATTCTCCACCGCGC
CTATGGTCCCTCTTGGAGCCAGCGTGGCGGGCCTGGCGGCTCCCGGGTGGTGAGAGAGCG
GTCCGGGAACG**ATG**AAGGCCTCGCAGTGCTGCTGCTGTCTCAGCCACCTCTTGGCTTCCG
TCCTCCTCCTGCTGTTGCTGCCTGAACTAAGCGGGCCCCTGGCAGTCCTGCTGCAGGCAG
CCGAGGCCGCGCCAGGTCTTGGGCCTCCTGACCCTAGACCACGGACATTACCGCCGCTGC
CACCGGGCCCTACCCCTGCCCAGCAGCCGGGCCGTGGTCTGGCTGAAGCTGCGGGGCCGC
GGGGCTCCGAGGGAGGCAATGGCAGCAACCCTGTGGCCGGGCTTGAGACGGACGATCACG
GAGGGAAGGCCGGGGAAGGCTCGGTGGGTGGCGGCCTTGCTGTGAGCCCCAACCCTGGCG
ACAAGCCCATGACCCAGCGGGCCCTGACCGTGTTGATGGTGGTGAGCGGCGCGGTGCTGG
TGTACTTCGTGGTCAGGACGGTCAGGATGAGAAGAAGAAACCGAAAGACTAGGAGATATG
GAGTTTTGGACACTAACATAGAAAATATGGAATTGACACCTTTAGAACAGGATGATGAGG
ATGATGACAACACGTTGTTTGATGCCAATCATCCTCGAAGA**TAA**GAATGTGCCTTTTGAT
GAAAGAACTTTATCTTTCTACAATGAAGAGTGGAATTTCTATGTTTAAGGAATAAGAAGC
CACTATATCAATGTTGGGGGGGTATTTAAGTTACATATATTTTAACAACCTTTAATTTGC
TGTTGCAATAAATACCGTATCCTTTTATTATATCTTTATATGTATAGAAGTACTCTATTA
ATGGGCTCAGAGATGTTGGGGATAAAGTATACTGTAATAATTTATCTGTTTGAAAATTAC
TATAAAACGGTGTTTTCTGGTCGGTTTTTGTTTCCTGCTTACCATATGATTGTAAATTGT
TTTATGTATTAATCAGTTAATGCTAATTATTTTTGCTGATGTCATATGTTAAAGAGCTAT
AAATTCCAACAACCAACTGGTGTGTAAAAATAATTTAAAATTTCCTTTACTGAAAGGTAT
TTCCCATTTTTGTGGGGAAAAGAAGCCAAATTTATTACTTTGTGTTGGGGTTTTTAAAAT
ATTAAGAAATGTCTAAGTTATTGTTTGCAAAACAATAAATATGATTTTAAATTCTCTTAA
AAAAAAAA

FIGURE 300

MKASQCCCCLSHLLASVLLLLLLPELSGPLAVLLQAAEAAPGLGPPDPRPRTLPPLPPGP
TPAQQPGRGLAEAAGPRGSEGGNGSNPVAGLETDDHGGKAGEGSVGGGLAVSPNPGDKPM
TQRALTVLMVVSGAVLVYFVVRTVRMRRRNRKTRRYGVLDTNIENMELTPLEQDDEDDDN
TLFDANHPRR

Signal peptide:
amino acids 1-28

Transmembrane domain:
amino acids 124-140

N-glycosylation site:
amino acids 83-87

N-myristoylation sites:
amino acids 69-75, 78-84, 81-87, 97-103, 103-109, 106-112, 157-160

FIGURE 301

CTCGGCTGGATTTAAGGTTGCCGCTAGCCGCCTGGGAATTTAAGGGACCCACACTACCTT
CCCGAAGTTGAAGGCAAGCGGTGATTGTTTGTAGACGGCGCTTTGTC<u>ATG</u>GGACCTGTGC
GGTTGGGAATATTGCTTTTCCTTTTTTTGGCCGTGCACGAGGCTTGGGCTGGGATGTTGA
AGGAGGAGGACGATGACACAGAACGCTTGCCCAGCAAATGCGAAGTGTGTAAGCTGCTGA
GCACAGAGCTACAGGCGGAACTGAGTCGCACCGGTCGATCTCGAGAGGTGCTGGAGCTGG
GGCAGGTGCTGGATACAGGCAAGAGGAAGAGACACGTGCCTTACAGCGTTTCAGAGACAA
GGCTGGAAGAGGCCTTAGAGAATTTATGTGAGCGGATCCTGGACTATAGTGTTCACGCTG
AGCGCAAGGGCTCACTGAGATATGCCAAGGGTCAGAGTCAGACCATGGCAACACTGAAAG
GCCTAGTGCAGAAGGGGGTGAAGGTGGATCTGGGGATCCCTCTGGAGCTTTGGGATGAGC
CCAGCGTGGAGGTCACATACCTCAAGAAGCAGTGTGAGACCATGTTGGAGGAGTTTGAAG
ACATTGTGGGAGACTGGTACTTCCACCATCAGGAGCAGCCCCTACAAAATTTTCTCTGTG
AAGGTCATGTGCTCCCAGCTGCTGAAACTGCATGTCTACAGGAAACTTGGACTGGAAAGG
AGATCACAGATGGGGAAGAGAAAACAGAAGGGGAGGAAGAGCAGGAGGAGGAGGAGGAAG
AGGAGGAAGAGGAAGGGGGAGACAAGATGACCAAGACAGGAAGCCACCCCAAACTTGACC
GAGAAGATCTT<u>TGA</u>CCCTTGCCTTTGAGCCCCCAGGAGGGGAAGGGATCATGGAGAGCCC
TCTAAAGCCTGCACTCTCCCTGCTCCACAGCTTTCAGGGTGTGTTTATGAGTGACTCCAC
CCAAGCTTGTAGCTGTTCTCTCCCATCTAACCTCAGGCAAGATCCTGGTGAAACAGCATG
ACATGGCTTCTGGGGTGGAGGGTGGGGGTGGAGGTCCTGCTCCTAGAGATGAACTCTATC
CAGCCCCTTAATTGGCAGGTGTATGTGCTGACAGTACTGAAAGCTTTCCTCTTTAACTGA
TCCCACCCCCACCCAAAAGTCAGCAGTGGCACTGGAGCTGTGGGCTTTGGGGAAGTCACT
TAGCTCCTTAAGGTCTGTTTTTAGACCCTTCCAAGGAAGAGGCCAGAACGGACATTCTCT
GCGATCTATATACATTGCCTGTATCCAGGAGGCTACACACCAGCAAACCGTGAAGGAGAA
TGGGACACTGGGTCATGGCCTGGAGTTGCTGATAATTTAGGTGGGATAGATACTTGGTCT
ACTTAAGCTCAATGTAACCCAGAGCCCACCATATAGTTTTATAGGTGCTCAACTTTCTAT
ATCGCTATTAAACTTTTTTCTTTTTTTCTA

FIGURE 302

MGPVRLGILLFLFLAVHEAWAGMLKEEDDDTERLPSKCEVCKLLSTELQAELSRTGRSRE
VLELGQVLDTGKRKRHVPYSVSETRLEEALENLCERILDYSVHAERKGSLRYAKGQSQTM
ATLKGLVQKGVKVDLGIPLELWDEPSVEVTYLKKQCETMLEEFEDIVGDWYFHHQEQPLQ
NFLCEGHVLPAAETACLQETWTGKEITDGEEKTEGEEEQEEEEEEEEEEEGGDKMTKTGSH
PKLDREDL

Important features of the protein:
Signal peptide:
amino acids 1-21

cAMP- and cGMP-dependent protein kinase phosphorylation site:
amino acids 106-110

N-myristoylation site:
amino acids 115-121

Amidation site:
amino acids 70-74

FIGURE 303

CTCCTGCACTAGGCTCTCAGCCAGGG**ATG**ATGCGCTGCTGCCGCCGCCGCTGCTGCTGCC
GGCAACCACCCCATGCCCTGAGGCCGTTGCTGTTGCTGCCCCTCGTCCTTTTACCTCCCC
TGGCAGCAGCTGCAGCGGGCCCAAACCGATGTGACACCATATACCAGGGCTTCGCCGAGT
GTCTCATCCGCTTGGGGGACAGCATGGGCCGCGGAGGCGAGCTGGAGACCATCTGCAGGT
CTTGGAATGACTTCCATGCCTGTGCCTCTCAGGTCCTGTCAGGCTGTCCGGAGGAGGCAG
CTGCAGTGTGGGAATCACTACAGCAAGAAGCTCGCCAGGCCCCCCGTCCGAATAACTTGC
ACACTCTGTGCGGTGCCCCGGTGCATGTTCGGGAGCGCGGCACAGGCTCCGAAACCAACC
AGGAGACGCTGCGGGCTACAGCGCCTGCACTCCCCATGGCCCCTGCGCCCCCACTGCTGG
CGGCTGCTCTGGCTCTGGCCTACCTCCTGAGGCCTCTGGCC**TAG**CTTGTTGGGTTGGGTA
GCAGCGCCCGTACCTCCAGCCCTGCTCTGGCGGTGGTTGTCCAGGCTCTGCAGAGCGCAG
CAGGGCTTTTCATTAAAGGTATTTATATTTGTA

FIGURE 304

MMRCCRRRCCCRQPPHALRPLLLLPLVLLPPLAAAAAGPNRCDTIYQGFAECLIRLGDSM
GRGGELETICRSWNDFHACASQVLSGCPEEAAAVWESLQQEARQAPRPNNLHTLCGAPVH
VRERGTGSETNQETLRATAPALPMAPAPPLLAAALALAYLLRPLA

Signal peptide:
Amino acids 1-35

Transmembrane domain:
Amino acids 141-157

N-myristoylation site:
Amino acids 127-133

Prokaryotic membrane lipoprotein lipid attachment site:
Amino acids 77-88

FIGURE 305

AAGTACTTGTGTCCGGGTGGTGGACTGGATTAGCTGCGGAGCCCTGGAAGCTGCCTGTCC
TTCTCCCTGTGCTTAACCAGAGGTGCCCATGGGTTGGACAATGAGGCTGGTCACAGCAGC
ACTGTTACTGGGTCTCATGATGGTGGTCACTGGAGACGAGGATGAGAACAGCCCGTGTGC
CCATGAGGCCCTCTTGGACGAGGACACCCTCTTTTGCCAGGGCCTTGAAGTTTTCTACCC
AGAGTTGGGGAACATTGGCTGCAAGGTTGTTCCTGATTGTAACAACTACAGACAGAAGAT
CACCTCCTGGATGGAGCCGATAGTCAAGTTCCCGGGGGCCGTGGACGGCGCAACCTATAT
CCTGGTGATGGTGGATCCAGATGCCCCTAGCAGAGCAGAACCCAGACAGAGATTCTGGAG
ACATTGGCTGGTAACAGATATCAAGGGCGCCGACCTGAAGAAAGGGAAGATTCAGGGCCA
GGAGTTATCAGCCTACCAGGCTCCCTCCCCACCGGCACACAGTGGCTTCCATCGCTACCA
GTTCTTTGTCTATCTTCAGGAAGGAAAAGTCATCTCTCTCCTTCCCAAGGAAAACAAAAC
TCGAGGCTCTTGGAAAATGGACAGATTTCTGAACCGCTTCCACCTGGGCGAACCTGAAGC
AAGCACCCAGTTCATGACCCAGAACTACCAGGACTCACCAACCCTCCAGGCTCCCAGAGG
AAGGGCCAGCGAGCCCAAGCACAAAACCAGGCAGAGATAGCTGCCTGCTAGATAGCCGGC
TTTGCCATCCGGGCATGTGGCCACACTGCTCACCACCGACGATGTGGGTATGGAACCCCC
TCTGGATACAGAACCCCTTCTTTTCCAATTAAAAAAAAAAATCATCAAA

FIGURE 306

MGWTMRLVTAALLLGLMMVVTGDEDENSPCAHEALLDEDTLFCQGLEVFYPELGNIGCKV
VPDCNNYRQKITSWMEPIVKFPGAVDGATYILVMVDPDAPSRAEPRQRFWRHWLVTDIKG
ADLKKGKIQGQELSAYQAPSPPAHSGFHRYQFFVYLQEGKVISLLPKENKTRGSWKMDRF
LNRFHLGEPEASTQFMTQNYQDSPTLQAPRGRASEPKHKTRQR

Important features of the protein:
Signal peptide:
amino acids 1-22

N-glycosylation site:
amino acids 169-173

Tyrosine kinase phosphorylation site:
amino acids 59-68

N-myristoylation sites:
amino acids 54-60, 83-89, 130-136

Phosphatidylethanolamine signature:
amino acids 113-157

FIGURE 307

AAGGAGCAGCCCGCAAGCACCAAGTGAGAGGC<u>ATG</u>AAGTTACAGTGTGTTTCCCTTTGGC
TCCTGGGTACAATACTGATATTGTGCTCAGTAGACAACCACGGTCTCAGGAGATGTCTGA
TTTCCACAGACATGCACCATATAGAAGAGAGTTTCCAAGAAATCAAAAGAGCCATCCAAG
CTAAGGACACCTTCCCAAATGTCACTATCCTGTCCACATTGGAGACTCTGCAGATCATTA
AGCCCTTAGATGTGTGCTGCGTGACCAAGAACCTCCTGGCGTTCTACGTGGACAGGGTGT
TCAAGGATCATCAGGAGCCAAACCCCAAAATCTTGAGAAAAATCAGCAGCATTGCCAACT
CTTTCCTCTACATGCAGAAAACTCTGCGGCAATGTCAGGAACAGAGGCAGTGTCACTGCA
GGCAGGAAGCCACCAATGCCACCAGAGTCATCCATGACAACTATGATCAGCTGGAGGTCC
ACGCTGCTGCCATTAAATCCCTGGGAGAGCTCGACGTCTTTCTAGCCTGGATTAATAAGA
ATCATGAAGTAATGTTCTCAGCT<u>TGA</u>TGACAAGGAACCTGTATAGTGATCCAGGGATGAA
CACCCCCTGTGCGGTTTACTGTGGGAGACAGCCCACCTTGAAGGGGAAGGAGATGGGGAA
GGCCCCTTGCAGCTGAAAGTCCCACTGGCTGGCCTCAGGCTGTCTTATTCCGCTTGAAAA
TAGGCAAAAAGTCTACTGTGGTATTTGTAATAAACTCTATCTGCTGAAAGGGCCTGCAGG
CCATCCTGGGAGTAAAGGGCTGCCTTCCCATCTAATTTATTGTAAAGTCATATAGTCCAT
GTCTGTGATGTGAGCCAAGTGATATCCTGTAGTACACATTGTACTGAGTGGTTTTTCTGA
ATAAATTCCATATTTTACCTATGA

FIGURE 308

MKLQCVSLWLLGTILILCSVDNHGLRRCLISTDMHHIEESFQEIKRAIQAKDTFPNVTIL
STLETLQIIKPLDVCCVTKNLLAFYVDRVFKDHQEPNPKILRKISSIANSFLYMQKTLRQ
CQEQRQCHCRQEATNATRVIHDNYDQLEVHAAAIKSLGELDVFLAWINKNHEVMFSA

Signal sequence:
amino acids 1-18

N-glycosylation sites:
amino acids 56-60, 135-139

cAMP- and cGMP-dependent protein kinase phosphorylation site:
amino acids 102-106

N-myristoylation site:
amino acids 24-30

Actinin-type actin-binding domain signature 1:
amino acids 159-169

FIGURE 309

GTCGACCCACGCGTCCGAAGCTGCTGGAGCCACGATTCAGTCCCCTGGACTGTAGATAAA
GACCCTTTCTTGCCAGGTGCTGAGACAACCACACT**ATG**AGAGGCACTCCAGGAGACGCTG
ATGGTGGAGGAAGGGCCGTCTATCAATCAATCACTGTTGCTGTTATCACATGCAAGTATC
CAGAGGCTCTTGAGCAAGGCAGAGGGGATCCCATTTATTTGGGAATCCAGAATCCAGAAA
TGTGTTTGTATTGTGAGAAGGTTGGAGAACAGCCCACATTGCAGCTAAAAGAGCAGAAGA
TCATGGATCTGTATGGCCAACCCGAGCCCGTGAAACCCTTCCTTTTCTACCGTGCCAAGA
CTGGTAGGACCTCCACCCTTGAGTCTGTGGCCTTCCCGGACTGGTTCATTGCCTCCTCCA
AGAGAGACCAGCCCATCATTCTGACTTCAGAACTTGGGAAGTCATACAACACTGCCTTTG
AATTAAATATAAATGAC**TGA**ACTCAGCCTAGAGGTGGCAGCTTGGTCTTTGTCTTAAAGT
TTCTGGTTCCCAATGTGTTTTCGTCTACATTTTCTTAGTGTCATTTTCACGCTGGTGCTG
AGACAGGAGCAAGGCTGCTGTTATCATCTCATTTTATAATGAAGAAGAAGCAATTACTTC
ATAGCAACTGAAGAACAGGATGTGGCCTCAGAAGCAGGAGAGCTGGGTGGTATAAGGCTG
TCCTCTCAAGCTGGTGCTGTGTAGGCCACAAGGCATCTGCATGAGTGACTTTAAGACTCA
AAGACCAAACACTGAGCTTTCTTCTAGGGGTGGGTATGAAGATGCTTCAGAGCTCATGCG
CGTTACCCACGATGGCATGACTAGCACAGAGCTGATCTCTGTTTCTGTTTTGCTTTATTC
CCTCTTGGGATGATATCATCCAGTCTTTATATGTTGCCAATATACCTCATTGTGTGTAAT
AGAACCTTCTTAGCATTAAGACCTTGTAAACAAAAATAATTCTTGGGGTGGGTATGAAGA
TGCTTCAGAGCTCATGCGCGTTACCCACGATGGCATGACTAGCACAGAGCTGATCTCTGT
TTCTGTTTTGCTTTATTCCCTCTTGGGATGATATCATCCAGTCTTTATATGTTGCCAATA
TACCTCATTGTGTGTAATAGAACCTTCTTAGCATTAAGACCTTGTAAACAAAAATAATTC
TTGTGTTAAGTTAAATCATTTTTGTCCTAATTGTAATGTGTAATCTTAAAGTTAAATAAA
CTTTGTGTATTTATATAATAATAAAGCTAAAACTGATATAAAATAAAGAAAGAGTAAACTG

FIGURE 310

MRGTPGDADGGGRAVYQSITVAVITCKYPEALEQGRGDPIYLGIQNPEMCLYCEKVGEQP
TLQLKEQKIMDLYGQPEPVKPFLFYRAKTGRTSTLESVAFPDWFIASSKRDQPIILTSEL
GKSYNTAFELNIND

Signal sequence:
amino acids 1-17

N-myristoylation site:
amino acids 10-16

Cell attachment sequence:
amino acids 36-39

FIGURE 311

GCGAGGCTGCACCAGCGCCTGGCACC**ATG**AGGACGCCTGGGCCTCTGCCCGTGCTGCTGC
TGCTCCTGGCGGGAGCCCCCGCCGCGCGGCCCACTCCCCCGACCTGCTACTCCCGCATGC
GGGCCCTGAGCCAGGAGATCACCCGCGACTTCAACCTCCTGCAGGTCTCGGAGCCCTCGG
AGCCATGTGTGAGATACCTGCCCAGGCTGTACCTGGACATACACAATTACTGTGTGCTGG
ACAAGCTGCGGGACTTTGTGGCCTCGCCCCCGTGTTGGAAAGTGGCCCAGGTAGATTCCT
TGAAGGACAAAGCACGGAAGCTGTACACCATCATGAACTCGTTCTGCAGGAGAGATTTGG
TATTCCTGTTGGATGACTGCAATGCCTTGGAATACCCAATCCCAGTGACTACGGTCCTGC
CAGATCGTCAGCGC**TAA**GGGAACTGAGACCAGAGAAAGAACCCAAGAGAACTAAAGTTAT
GTCAGCTACCCAGACTTAATGGGCCAGAGCCATGACCCTCACAGGTCTTGTGTTAGTTGT
ATCTGAAACTGTTATGTATCTCTCTACCTTCTGGAAAACAGGGCTGGTATTCCTACCCAG
GAACCTCCTTTGAGCATAGAGTTAGCAACCATGCTTCTCATTCCCTTGACTCATGTCTTG
CCAGGATGGTTAGATACACAGCATGTTGATTTGGTCACTAAAAAGAAGAAAAGGACTAAC
AAGCTTCACTTTTATGAACAACTATTTTGAGAACATGCACAATAGTATGTTTTTATTACT
GGTTTAATGGAGTAATGGTACTTTTATTCTTTCTTGATAGAAACCTGCTTACATTTAACC
AAGCTTCTATTATGCCTTTTTCTAACACAGACTTTCTTCACTGTCTTTCATTTAAAAAGA
AATTAATGCTCTTAAGATATATATTTTACGTAGTGCTGACAGGACCCACTCTTTCATTGA
AAGGTGATGAAAATCAAATAAAGAATCTCTTCACATGGA

FIGURE 312

MRTPGPLPVLLLLLAGAPAARPTPPTCYSRMRALSQEITRDFNLLQVSEPSEPCVRYLPR
LYLDIHNYCVLDKLRDFVASPPCWKVAQVDSLKDKARKLYTIMNSFCRRDLVFLLDDCNA
LEYPIPVTTVLPDRQR

Important features of the protein:
Signal peptide:
amino acids 1-19

Tyrosine kinase phosphorylation site:
amino acids 60-69

N-myristoylation site:
amino acids 16-22

FIGURE 313

GAGCGACGCTGTCTCTAGTCGCTGATCCCAA<u>**ATG**</u>CACCGGCTCATCTTTGTCTACACTCT
AATCTGCGCAAACTTTTGCAGCTGTCGGGACACTTCTGCAACCCCGCAGAGCGCATCCAT
CAAAGCTTTGCGCAACGCCAACCTCAGGCGAGATGACTTGTACCGAAGAGATGAGACCAT
CCAGGTGAAAGGAAACGGCTACGTGCAGAGTCCTAGATTCCCGAACAGCTACCCCAGGAA
CCTGCTCCTGACATGGCGGCTTCACTCTCAGGAGAATACACGGATACAGCTAGTGTTTGA
CAATCAGTTTGGATTAGAGGAAGCAGAAAATGATATCTGTAGGTATGATTTTGTGGAAGT
TGAAGATATATCCGAAACCAGTACCATTATTAGAGGACGATGGTGTGGACACAAGGAAGT
TCCTCCAAGGATAAAATCAAGAACGAACCAAATTAAAATCACATTCAAGTCCGATGACTA
CTTTGTGGCTAAACCTGGATTCAAGATTTATTATTCTTTGCTGGAAGATTTCCAACCCGC
AGCAGCTTCAGAGACCAACTGGGAATCTGTCACAAGCTCTATTTCAGGGGTATCCTATAA
CTCTCCATCAGTAACGGATCCCACTCTGATTGCGGATGCTCTGGACAAAAAAATTGCAGA
ATTTGATACAGTGGAAGATCTGCTCAAGTACTTCAATCCAGAGTCATGGCAAGAAGATCT
TGAGAATATGTATCTGGACACCCCTCGGTATCGAGGCAGGTCATACCATGACCGGAAGTC
AAAAGTTGACCTGGATAGGCTCAATGATGATGCCAAGCGTTACAGTTGCACTCCCAGGAA
TTACTCGGTCAATATAAGAGAAGAGCTGAAGTTGGCCAATGTGGTCTTCTTTCCACGTTG
CCTCCTCGTGCAGCGCTGTGGAGGAAATTGTGGCTGTGGAACTGTCAACTGGAGGTCCTG
CACATGCAATTCAGGGAAAACCGTGAAAAAGTATCATGAGGTATTACAGTTTGAGCCTGG
CCACATCAAGAGGAGGGGTAGAGCTAAGACCATGGCTCTAGTTGACATCCAGTTGGATCA
CCATGAACGATGCGATTGTATCTGCAGCTCAAGACCACCTCGA<u>**TAA**</u>GAGAATGTGCACAT
CCTTACATTAAGCCTGAGAGAA

FIGURE 314

MHRLIFVYTLICANFCSCRDTSATPQSASIKALRNANLRRDDLYRRDETIQVKGNGYVQS
PRFPNSYPRNLLLTWRLHSQENTRIQLVFDNQFGLEEAENDICRYDFVEVEDISETSTII
RGRWCGHKEVPPRIKSRTNQIKITFKSDDYFVAKPGFKIYYSLLEDFQPAAASETNWESV
TSSISGVSYNSPSVTDPTLIADALDKKIAEFDTVEDLLKYFNPESWQEDLENMYLDTPRY
RGRSYHDRKSKVDLDRLNDDAKRYSCTPRNYSVNIREELKLANVVFFPRCLLVQRCGGNC
GCGTVNWRSCTCNSGKTVKKYHEVLQFEPGHIKRRGRAKTMALVDIQLDHHERCDCICSS
RPPR

Signal peptide:
amino acids 1-18

N-glycosylation site:
amino acids 270-274

cAMP- and cGMP-dependent protein kinase phosphorylation site:
amino acids 262-266

Tyrosine kinase phosphorylation site:
amino acids 256-265

N-myristoylation sites:
amino acids 94-100, 186-192, 297-303, 298-304

TonB-dependent receptor proteins signature 1:
amino acids 1-56

FIGURE 315

CGGCTCGAGGCTCCCGCCAGGAGAAAGGAACATTCTGAGGGGAGTCTACACCCTGTGGAG
CTCAAG**ATG**GTCCTGAGTGGGGCGCTGTGCTTCCGAATGAAGGACTCGGCATTGAAGGTG
CTTTATCTGCATAATAACCAGCTTCTAGCTGGAGGGCTGCATGCAGGGAAGGTCATTAAA
GGTGAAGAGATCAGCGTGGTCCCCAATCGGTGGCTGGATGCCAGCCTGTCCCCCGTCATC
CTGGGTGTCCAGGGTGGAAGCCAGTGCCTGTCATGTGGGGTGGGGCAGGAGCCGACTCTA
ACACTAGAGCCAGTGAACATCATGGAGCTCTATCTTGGTGCCAAGGAATCCAAGAGCTTC
ACCTTCTACCGGCGGGACATGGGGCTCACCTCCAGCTTCGAGTCGGCTGCCTACCCGGGC
TGGTTCCTGTGCACGGTGCCTGAAGCCGATCAGCCTGTCAGACTCACCCAGCTTCCCGAG
AATGGTGGCTGGAATGCCCCCATCACAGACTTCTACTTCCAGCAGTGTGAC**TAG**GGCAAC
GTGCCCCCCAGAACTCCCTGGGCAGAGCCAGCTCGGGTGAGGGGTGAGTGGAGGAGACCC
ATGGCGGACAATCACTCTCTCTGCTCTCAGGACCCCCACGTCTGACTTAGTGGGCACCTG
ACCACTTTGTCTTCTGGTTCCCAGTTTGGATAAATTCTGAGATTTGGAGCTCAGTCCACG
GTCCTCCCCCACTGGATGGTGCTACTGCTGTGGAACCTTGTAAAAACCATGTGGGGTAAA
CTGGGAATAACATGAAAAGATTTCTGTGGGGGTGGGGTGGGGGAGTGGTGGGAATCATTC
CTGCTTAATGGTAACTGACAAGTGTTACCCTGAGCCCCGCAGGCCAACCCATCCCCAGTT
GAGCCTTATAGGGTCAGTAGCTCTCCACATGAAGTCCTGTCACTCACCACTGTGCAGGAG
AGGGAGGTGGTCATAGAGTCAGGGATCTATGGCCCTTGGCCCAGCCCCACCCCCTTCCCT
TTAATCCTGCCACTGTCATATGCTACCTTTCCTATCTCTTCCCTCATCATCTTGTTGTGG
GCATGAGGAGGTGGTGATGTCAGAAGAAATGGCTCGAGCTCAGAAGATAAAAGATAAGTA
GGGTATGCTGATCCTCTTTTAAAAACCCAAGATACAATCAAAATCCCAGATGCTGGTCTC
TATTCCCATGAAAAAGTGCTCATGACATATTGAGAAGACCTACTTACAAAGTGGCATATA
TTGCAATTTATTTTAATTAAAAGATACCTATTTATATATTTCTTTATAGAAAAAAGTCTG
GAAGAGTTTACTTCAATTGTAGCAATGTCAGGGTGGTGGCAGTATAGGTGATTTTTCTTT
TAATTCTGTTAATTTATCTGTATTTCCTAATTTTTCTACAATGAAGATGAATTCCTTGTA
TAAAAATAAGAAAAGAAATTAATCTTGAGGTAAGCAGAGCAGACATCATCTCTGATTGTC
CTCAGCCTCCACTTCCCCAGAGTAAATTCAAATTGAATCGAGCTCTGCTGCTCTGGTTGG
TTGTAGTAGTGATCAGGAAACAGATCTCAGCAAAGCCACTGAGGAGGAGGCTGTGCTGAG
TTTGTGTGGCTGGAATCTCTGGGTAAGGAACTTAAAGAACAAAAATCATCTGGTAATTCT
TTCCTAGAAGGATCACAGCCCCTGGGATTCCAAGGCATTGGATCCAGTCTCTAAGAAGGC
TGCTGTACTGGTTGAATTGTGTCCCCCTCAAATTCACATCCTTCTTGGAATCTCAGTCTG
TGAGTTTATTTGGAGATAAGGTCTCTGCAGATGTAGTTAGTTAAGACAAGGTCATGCTGG
ATGAAGGTAGACCTAAATTCAATATGACTGGTTTCCTTGTATGAAAAGGAGAGGACACAG
AGACAGAGGAGACGCGGGGAAGACTATGTAAAGATGAAGGCAGAGATCGGAGTTTTGCAG
CCACAAGCTAAGAAACACCAAGGATTGTGGCAACCATCAGAAGCTTGGAAGAGGCAAAGA
AGAATTCTTCCCTAGAGGCTTTAGAGGGATAACGGCTCTGCTGAAACCTTAATCTCAGAC
TTCCAGCCTCCTGAACGAAGAAAGAATAAATTTCGGCTGTTTTAAGCCACCAAGGATAAT
TGGTTACAGCAGCTCTAGGAAACTAATACAGCTGCTAAAATGATCCCTGTCTCCTCGTGT
TTACATTCTGTGTGTGTGTCCCCTCCCACAATGTACCAAAGTTGTCTTTGTGACCAATAGAA
TATGGCAGAAGTGATGGCATGCCACTTCCAAGATTAGGTTATAAAAGACACTGCAGCTTC
TACTTGAGCCCTCTCTCTCTGCCACCCACCGCCCCCAATCTATCTTGGCTCACTCGCTCT
GGGGGAAGCTAGCTGCCATGCTATGAGCAGGCCTATAAAGAGACTTACGTGGTAAAAAAT
GAAGTCTCCTGCCCACAGCCACATTAGTGAACCTAGAAGCAGAGACTCTGTGAGATAATC
GATGTTTGTTGTTTTAAGTTGCTCAGTTTTGGTCTAACTTGTTATGCAGCAATAGATAAA
TAATATGCAGAGAAAGAG

FIGURE 316

MVLSGALCFRMKDSALKVLYLHNNQLLAGGLHAGKVIKGEEISVVPNRWLDASLSPVILG
VQGGSQCLSCGVGQEPTLTLEPVNIMELYLGAKESKSFTFYRRDMGLTSSFESAAYPGWF
LCTVPEADQPVRLTQLPENGGWNAPITDFYFQQCD

N-myristoylation sites:
amino acids 29-34, 30-35, 60-65, 63-68, 73-78, 91-96, 106-111

Interleukin-1 signature:
amino acids 111-131

Interleukin-1 proteins:
amino acids 8-29, 83-120, 95-134, 64-103

FIGURE 317

<u>ATG</u>GAACTTGGACTTGGAGGCCTCTCCACGCTGTCCCACTGCCCCTGGCCTAGGCGGCAG
CCTGCCCTGTGGCCCACCCTGGCCGCTCTGGCTCTGCTGAGCAGCGTCGCAGAGGCCTCC
CTGGGCTCCGCGCCCCGCAGCCCTGCCCCCCGCGAAGGCCCCCCGCCTGTCCTGGCGTCC
CCCGCCGGCCACCTGCCGGGGGGACGCACGGCCCGCTGGTGCAGTGGAAGAGCCCGGCGG
CCGCCGCCGCAGCCTTCTCGGCCCGCGCCCCCGCCGCCTGCACCCCCATCTGCTCTTCCC
CGCGGGGGCCGCGCGGCGCGGGCTGGGGGCCCGGGCAGCCGCGCTCGGGCAGCGGGGGCG
CGGGGCTGCCGCCTGCGCTCGCAGCTGGTGCCGGTGCGCGCGCTCGGCCTGGGCCACCGC
TCCGACGAGCTGGTGCGTTTCCGCTTCTGCAGCGGCTCCTGCCGCCGCGCGCGCTCTCCA
CACGACCTCAGCCTGGCCAGCCTACTGGGCGCCGGGGCCCTGCGACCGCCCCCGGGCTCC
CGGCCCGTCAGCCAGCCCTGCTGCCGACCCACGCGCTACGAAGCGGTCTCCTTCATGGAC
GTCAACAGCACCTGGAGAACCGTGGACCGCCTCTCCGCCACCGCCTGCGGCTGCCTGGGC
<u>TGA</u>

FIGURE 318

MELGLGGLSTLSHCPWPRRQPALWPTLAALALLSSVAEASLGSAPRSPAPREGPPPVLAS
PAGHLPGGRTARWCSGRARRPPPQPSRPAPPPPAPPSALPRGGRAARAGGPGSRARAAGA
RGCRLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLSLASLLGAGALRPPPGS
RPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG

signal sequence:
Amino acids 1-39

N-glycosylation site:
Amino acids 202-206

N-myristoylation sites:
Amino acids 6-12;67-73;102-108;109-115;119-125

FIGURE 319

GTTGCTATGTTGCCCAGGCTGGTCTTGAAGTGCCTTGACCTCCTAAAGTGTTGGAACCAC
AGACGTGAGCCACTCCACCCAGCCTAAAACTTCATCTTCTTTGGATGAGATGAACACTTT
TAACAAGAGAACAGGACTCTATATAAATCGCTGTGGGCTCACCACCTCTAAGGAGGAGCA
CTGACTGAAGACAGAAAAATTGATGAACTGAAGAAGACATGGTCCATTATGCCTTACAAA
CTTACACAGTGCTTTGGGAATTCCAAAGTACTCAGTGGAGAGAGGTGTTTCAGGAGCCGT
AGAGCCAGATCGTCATC**ATG**TCTGCATTGTGGCTGCTGCTGGGCCTCCTTGCCCTGATGG
ACTTGTCTGAAAGCAGCAACTGGGGATGCTATGGAAACATCCAAAGCCTGGACACCCCTG
GAGCATCTTGTGGGATTGGAAGACGTCACGGCCTGAACTACTGTGGAGTTCGTGCTTCTG
AAAGGCTGGCTGAAATAGACATGCCATACCTCCTGAAATATCAACCCATGATGCAAACCA
TTGGCCAAAAGTACTGCATGGATCCTGCCGTGATCGCTGGTGTCTTGTCCAGGAAGTCTC
CCGGTGACAAAATTCTGGTCAACATGGGCGATAGGACTAGCATGGTGCAGGACCCTGGCT
CTCAAGCTCCCACATCCTGGATTAGTGAGTCTCAGGTTTCCCAGACAACTGAAGTTCTGA
CTACTAGAATCAAAGAAATCCAGAGGAGGTTTCCAACCTGGACCCCTGACCAGTACCTGA
GAGGTGGACTCTGTGCCTACAGTGGGGGTGCTGGCTATGTCCGAAGCAGCCAGGACCTGA
GCTGTGACTTCTGCAATGATGTCCTTGCACGAGCCAAGTACCTCAAGAGACATGGCTTC**T**
AACATCTCAGATGAAACCCAAGACCATGATCACATATGCAGCCTCAAATGTTACACAGAT
AAAACTAGCCAAGGGCACCTGTAACTGGGAATCTGAGTTTGACCTAAAAGTCATTAAAAT
AACATGAATCCCATTAAAAAAAAAAAAAA

FIGURE 320

MSALWLLLGLLALMDLSESSNWGCYGNIQSLDTPGASCGIGRRHGLNYCGVRASERLAEI
DMPYLLKYQPMMQTIGQKYCMDPAVIAGVLSRKSPGDKILVNMGDRTSMVQDPGSQAPTS
WISESQVSQTTEVLTTRIKEIQRRFPTWTPDQYLRGGLCAYSGGAGYVRSSQDLSCDFCN
DVLARAKYLKRHGF

Important features of the protein:
Signal peptide:
amino acids 1-19

N-myristoylation sites:
amino acids 23-29, 26-32, 35-41, 45-51, 50-56, 76-82, 156-162

Amidation site:
amino acids 40-44

FIGURE 321

GCCTTATAAAGTAGCCTCTGCATCTGCCTGCCTCGGGCAGAGGAGGGCTACCCTGGGGCT
GAGAGTTCACCTGTCTCAGGAACCACCTGAGCCCACAGATCCTGTGGGCAGCGGCCAGGG
CAGCC**ATG**GCTTGGGCAAGTAGGCTGGGCCTGCTGCTGGCACTGCTGCTGCCCGTGGTCG
GTGCCTCCACGCCAGGCACCGTGGTCCGACTCAACAAGGCAGCATTGAGCTACGTGTCTG
AAATTGGGAAAGCCCCTCTCCAGCGGGCCCTGCAGGTCACTGTCCCTCATTTCCTGGACT
GGAGTGGAGAGGCGCTTCAGCCCACCAGGATCCGGATTCTGAATGTCCATGTGCCCCGCC
TCCACCTGAAATTCATTGCTGGTTTCGGAGTGCGCCTGCTGGCAGCAGCTAATTTTACTT
TCAAGGTCTTTCGCGCCCCAGAGCCCCTGGAGCTGACGCTGCCTGTGGAACTGCTGGCTG
ACACCCGCGTGACCCAGAGCTCCATCAGGACCCCTGTGGTCAGCATCTCTGCCTGCTCTT
TATTCTCGGGCCACGCCAACGAGTTTGATGGCAGTAACAGCACCTCCCACGCGCTGCTGG
TCCTGGTGCAGAAGCACATTAAAGCTGTCTTGAGTAACAAGCTGTGCCTGAGCATCTCCA
ACCTGGTGCAGGGTGTCAATGTCCACCTGGGCACCTTAATTGGCCTCAACCCCGTGGGTC
CTGAGTCCCAGATCCGCTATTCCATGGTCAGTGTGCCCACTGTCACCAGTGACTACATTT
CCCTGGAAGTCAATGCTGTTCTCTTCCTGCTGGGCAACCCCATCATCCTGCCCACGGATG
CCACCCCTTTTGTGTTGCCAAGGCATGTGGGTACCGAGGGCTCCATGGCCACCGTGGGCC
TCTCCCAGCAGCTGTTTGACTCTGCGCTCCTGCTGCTGCAGAAGGCCGGTGCCCTCAACC
TGGACATCACAGGGCAGCTGAGGTCGGATGACAACCTGCTGAACACCTCTGCTCTGGGCC
GGCTCATCCCGGAGGTGGCCCGCCAGTTTCCCGAGCCCATGCCTGTGGTGCTCAAGGTGC
GGCTGGGTGCCACACCTGTGGCCATGCTCCACACAAACAACGCCACCCTGCGGCTGCAGC
CCTTCGTGGAGGTCCTGGCCACAGCCTCCAACTCGGCTTTCCAGTCCCTCTTCTCCCTGG
ATGTGGTAGTGAACTTGAGACTCCAGCTCTCTGTGTCCAAGGTGAAGCTTCAGGGGACCA
CGTCTGTGCTGGGGGATGTCCAGCTCACGGTGGCCTCCTCCAACGTGGGCTTCATTGATA
CAGATCAGGTGCGCACACTGATGGGCACCGTTTTTGAGAAGCCCCTGCTGGACCATCTCA
ATGCTCTCTTGGCCATGGGAATTGCCCTCCCTGGTGTGGTCAACCTCCACTATGTTGCCC
CTGAGATCTTTGTCTATGAGGGCTACGTGGTGATATCCAGTGGACTCTTCTACCAGAGC**T**
GAGGCAAGACCACTGGGAGGCCTGAGAGTGGGCCAGCTCGCTGCTCAGGCGAATTTCTCA
TTTCAAGCCACTGGGGAAACTGAGGCAAAACCATACTTAGTCATCACCAACAAGCTGGAC
TGCTTAGCTGGGCTGTTTTATCTTCCCTGAGTGCCTGGGTCTCCCTCCCTCACTTCTGCC
CTTTCCCTTCCTCCTCCTCTTCTCCTCCCTCTTCCCTCATCTCCCCCCTCCTTCCTCTGC
CCCACCCCAGGGGGGAGCAGACTGCTCCTCCAGGCTGTATAGACCTGCCCTCTTGCATTA
AACAACTTCTCTTGAGCTGC

FIGURE 322

MAWASRLGLLLALLLPVVGASTPGTVVRLNKAALSYVSEIGKAPLQRALQVTVPHFLDWS
GEALQPTRIRILNVHVPRLHLKFIAGFGVRLLAAANFTFKVFRAPEPLELTLPVELLADT
RVTQSSIRTPVVSISACSLFSGHANEFDGSNSTSHALLVLVQKHIKAVLSNKLCLSISNL
VQGVNVHLGTLIGLNPVGPESQIRYSMVSVPTVTSDYISLEVNAVLFLLGNPIILPTDAT
PFVLPRHVGTEGSMATVGLSQQLFDSALLLLQKAGALNLDITGQLRSDDNLLNTSALGRL
IPEVARQFPEPMPVVLKVRLGATPVAMLHTNNATLRLQPFVEVLATASNSAFQSLFSLDV
VVNLRLQLSVSKVKLQGTTSVLGDVQLTVASSNVGFIDTDQVRTLMGTVFEKPLLDHLNA
LLAMGIALPGVVNLHYVAPEIFVYEGYVVISSGLFYQS

Important features of the protein:
Signal peptide:
Amino acids 1-20

Transmembrane domain:
Amino acids 217-236

N-glycosylation sites:
Amino acids 96-100;151-155;293-297;332-336

N-myristoylation sites:
Amino acids 8-14;149-155;189-195;249-255;252-258;283-289

LBP / BPI / CETP family proteins:
Amino acids 22-50; 251-287

FIGURE 323

TTGAAAATCTACTCTATCAGCTGCTGTGGTTGCCACCATTCTCAGGACCCTCGCC**ATG**AA
AGCCCTTATGCTGCTCACCCTGTCTGTTCTGCTCTGCTGGGTCTCAGCTGACATTCGCTG
TCACTCCTGCTACAAGGTCCCTGTGCTGGGCTGTGTGGACCGGCAGTCCTGCCGCCTGGA
GCCAGGACAGCAATGCCTGACAACACATGCATACCTTGGTAAGATGTGGGTTTTCTCCAA
TCTGCGCTGTGGCACACCAGAAGAGCCCTGTCAGGAGGCCTTCAACCAAACCAACCGCAA
GCTGGGTCTGACATATAACACCACCTGCTGCAACAAGGACAACTGCAACAGCGCAGGACC
CCGGCCCACTCCAGCCCTGGGCCTTGTCTTCCTTACCTCCTTGGCTGGCCTTGGCCTCTG
GCTGCTGCAC**TGA**GACTCATTCCATTGGCTGCCCCTCCTCCCACCTGCCTTGGCCTGAGC
CTCTCTCCCTGTGTCTCTGTATCCCCTGGCTTTACAGAATCGTCTCTCCCTAGCTCCCAT
TTCTTTAATTAAACACTGTTCCGAGTGGTCTCCTCATCCATCCTTCCCACCTCACACCCT
TCACTCTCCTTTTTCTGGGTCCCTTCCCACTTCCTTCCAGGACCTCCATTGGCTCCTAGA
AGGGCTCCCCACTTTGCTTCCTATACTCTGCTGTCCCCTACTTGAGGAGGGATTGGGATC
TGGGCCTGAAATGGGGCTTCTGTGTTGTCCCCAGTGAAGGCTCCCACAAGGACCTGATGA
CCTCACTGTACAGAGCTGACTCCCCAAACCCAGGCTCCCATATGTACCCCATCCCCCATA
CTCACCTCTTTCCATTTTGAGTAATAAATGTCTGAGTCTGGAAAAAAAAAAAAAAAAAA

FIGURE 324

MKALMLLTLSVLLCWVSADIRCHSCYKVPVLGCVDRQSCRLEPGQQCLTTHAYLGKMWVF
SNLRCGTPEEPCQEAFNQTNRKLGLTYNTTCCNKDNCNSAGPRPTPALGLVFLTSLAGLG
LWLLH

Important features of the protein:
Signal peptide:
amino acids 1-18

N-glycosylation sites:
amino acids 77-81, 88-92

N-myristoylation site:
amino acids 84-90

Ly-6 / u-PAR domain protein signature:
amino acids 85-98

FIGURE 325

ACGGGCCGCAGCGGCAGTGACGTAGGGTTGGCGÇACGGATCCGTTGCGGCTGCAGCTCTG
CAGTCGGGCCGTTCCTTCGCCGCCGCCAGGGGTAGCGGTGTAGCTGCGCAGCGTCGCGCG
CGCTACCGCACCCAGGTTCGGCCCGTAGGCGTCTGGCAGCCCGGCGCCATCTTCATCGAG
CGCC**ATG**GCCGCAGCCTGCGGGCCGGGAGCGGCCGGGTACTGCTTGCTCCTCGGCTTGCA
TTTGTTTCTGCTGACCGCGGGCCCTGCCCTGGGCTGGAACGACCCTGACAGAATGTTGCT
GCGGGATGTAAAAGCTCTTACCCTCCACTATGACCGCTATACCACCTCCCGCAGGCTGGA
TCCCATCCCACAGTTGAAATGTGTTGGAGGCACAGCTGGTTGTGATTCTTATACCCCAAA
AGTCATACAGTGTCAGAACAAAGGCTGGGATGGGTATGATGTACAGTGGGAATGTAAGAC
GGACTTAGATATTGCATACAAATTTGGAAAAACTGTGGTGAGCTGTGAAGGCTATGAGTC
CTCTGAAGACCAGTATGTACTAAGAGGTTCTTGTGGCTTGGAGTATAATTTAGATTATAC
AGAACTTGGCCTGCAGAAACTGAAGGAGTCTGGAAAGCAGCACGGCTTTGCCTCTTTCTC
TGATTATTATTATAAGTGGTCCTCGGCGGATTCCTGTAACATGAGTGGATTGATTACCAT
CGTGGTACTCCTTGGGATCGCCTTTGTAGTCTATAAGCTGTTCCTGAGTGACGGGCAGTA
TTCTCCTCCACCGTACTCTGAGTATCCTCCATTTTCCCACCGTTACCAGAGATTCACCAA
CTCAGCAGGACCTCCTCCCCCAGGCTTTAAGTCTGAGTTCACAGGACCACAGAATACTGG
CCATGGTGCAACTTCTGGTTTTGGCAGTGCTTTTACAGGACAACAAGGATATGAAAATTC
AGGACCAGGGTTCTGGACAGGCTTGGGAACTGGTGGAATACTAGGATATTTGTTTGGCAG
CAATAGAGCGGCAACACCCTTCTCAGACTCGTGGTACTACCCGTCCTATCCTCCCTCCTA
CCCTGGCACGTGGAATAGGGCTTACTCACCCCTTCATGGAGGCTCGGGCAGCTATTCGGT
ATGTTCAAACTCAGACACGAAAACCAGAACTGCATCAGGATATGGTGGTACCAGGAGACG
A**TAA**AGTAGAAAGTTGGAGTCAAACACTGGATGCAGAAATTTTGGATTTTTCATCACTTT
CTCTTTAGAAAAAAAGTACTACCTGTTAACAATTGGGAAAAGGGGATATTCAAAAGTTCT
GTGGTGTTATGTCCAGTGTAGCTTTTTGTATTCTATTATTTGAGGCTAAAAGTTGATGTG
TGACAAAATACTTATGTGTTGTATGTCAGTGTAACATGCAGATGTATATTGCAGTTTTTG
AAAGTGATCATTACTGTGGAATGCTAAAAATACATTAATTTCTAAAACCTGTGATGCCCT
AAGAAGCATTAAGAATGAAGGTGTTGTACTAATAGAAACTAAGTACAGAAAATTTCAGTT
TTAGGTGGTTGTAGCTGATGAGTTATTACCTCATAGAGACTATAATATTCTATTTGGTAT
TATATTATTTGATGTTTGCTGTTCTTCAAACATTTAAATCAAGCTTTGGACTAATTATGC
TAATTTGTGAGTTCTGATCACTTTTGAGCTCTGAAGCTTTGAATCATTCAGTGGTGGAGA
TGGCCTTCTGGTAACTGAATATTACCTTCTGTAGGAAAAGGTGGAAAATAAGCATCTAGA
AGGTTGTTGTGAATGACTCTGTGCTGGCAAAAATGCTTGAAACCTCTATATTTCTTTCGT
TCATAAGAGGTAAAGGTCAAATTTTTCAACAAAAGTCTTTTAATAACAAAAGCATGCAGT
TCTCTGTGAAATCTCAAATATTGTTGTAATAGTCTGTTTCAATCTTAAAAAGAATCA

FIGURE 326

MAAACGPGAAGYCLLLGLHLFLLTAGPALGWNDPDRMLLRDVKALTLHYDRYTTSRRLDP
IPQLKCVGGTAGCDSYTPKVIQCQNKGWDGYDVQWECKTDLDIAYKFGKTVVSCEGYESS
EDQYVLRGSCGLEYNLDYTELGLQKLKESGKQHGFASFSDYYYKWSSADSCNMSGLITIV
VLLGIAFVVYKLFLSDGQYSPPPYSEYPPFSHRYQRFTNSAGPPPPGFKSEFTGPQNTGH
GATSGFGSAFTGQQGYENSGPGFWTGLGTGGILGYLFGSNRAATPFSDSWYYPSYPPSYP
GTWNRAYSPLHGGSGSYSVCSNSDTKTRTASGYGGTRRR

Signal peptide:
amino acids 1-30

Transmembrane domain:
amino acids 171-190

N-glycosylation site:
amino acids 172-176

Glycosaminoglycan attachment sites:
amino acids 244-248, 259-263, 331-335

Tyrosine kinase phosphorylation site:
amino acids 98-106

N-myristoylation sites:
amino acids 68-74, 69-75, 131-137, 241-247, 247-253, 266-272, 270-276, 278-284, 312-318

FIGURE 327

GGCACGAGGTGGAAGGGCTTTTACAAACAGATTGCTGGCCCCACCCCCCAGAATTTCTCA
TCAGGAGTGGGCAAGACCAATCATTTGCATTTCTGACAAGTTCCCAGGAGCTGCAGCTGC
TGGCCCTGGAACCACACTTTGAGAACCACTGCTTTAGACCAAACACCAAAGGAAGATGCA
GCCACCCTCCTTTACATGTCACAACGCTCAGGGTCCATGAGTACCTCAGGCTGTCCAGCT
GAGCTCCACCTGCAGCAGCCGAGATTCCCGACTCGCTCCACCATTGGGGGCTAGGAGTGA
AGCGTGTCACC**ATG**GTCAGCTCATGGCCAGCCAGGAAAGCCTCTCTGCTGTGCGTCTGTG
CAGTTCTTGTTCTTCCCTGGAGGACTCTTGGATCGCCTGTGATCTTGGCCAGGAGACCAG
GTGCCTGGGTCCCTTCCTGGAAGGGGACAAGTTACACACCCCAGCCCCATTTTCCCACCA
ACTTCTACATGCCTTGGGAGAACCTTCTACATGTTGGCTGCCCCCTTCCCCTATTTCAGC
AGTGCCCAGTCCTGCTTATAAACCTGAGGCCTGCTCCCCATACCTTCCCTGTGCAAGTGC
CAGCCGTTATTCCAGGCAGCCCAATGTTGTTGAGGCCAGATGGATTCCTGGAAGCAGCTG
GCCCATGGATG**TGA**GTCATCACAGTATTCTAGAAACAGAGAAGAGGTCTTAACCTAATGC
GCATAGAGAAATTGTTCTCATTGTAAACATACCCCTGTCCTTAGCTGATCTAGGTGGAAG
CCCAGCTTCATGTGCTAGGGGGCATGATAATGATAATAAAGGAATTGTATCTAGGACTAA

FIGURE 328

MVSSWPARKASLLCVCAVLVLPWRTLGSPVILARRPGAWVPSWKGTSYTPQPHFPTNFYM
PWENLLHVGCPLPLFQQCPVLLINLRPAPHTFPVQVPAVIPGSPMLLRPDGFLEAAGPWM

Signal peptide:
amino acids 1-27

cAMP- and cGMP-dependent protein kinase phosphorylation site:
amino acids 8-12

FIGURE 329

CAAAGAGTAGTCAGTCCCTTCTTGGCTCTGCTGACACTCGAGCCCACATTCCATCACCTG
CTCCCAATC**ATG**CAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTC
TGCAACCAGGTCCTCTCTGCACCACTTGCTGCTGACACGCCGACCGCCTGCTGCTTCAGC
TACACCTCCCGACAGATTCCACAGAATTTCATAGCTGACTACTTTGAGACGAGCAGCCAG
TGCTCCAAGCCCAGTGTCATCTTCCTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCCC
AGTGAGGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCC**TGA**GGGGTCCAG
AAGCTTCGAGGCCCAGCGACCTCAGTGGGCCCAGTGGGGAGGAGCAGGAGCCTGAGCCTT
GGGAACATGCGTGTGACCTCTACAGCTACCTCTTCTATGGACTGGTTATTGCCAAACAGC
CACACTGTGGGACTCTTCTTAACTTAAATTTTAATTTATTTATACTATTTAGTTTTTATA
ATTTATTTTTGATTTCACAGTGTGTTTGTGATTGTTTGCTCTGAGAGTTCCCCCTGTCCC
CTCCCCCTTCCCTCACAGTGTGTCTGGTGACAACCGAGTGGCTGTCATCGGCCTGTGTAG
GCAGTCATGGCACCAAAGCCACCAGACTGACAAATGTGTATCAAATGCTTTTGTTCAGGG
CTGTGATCGGCCTGGGGAAATAATAAAGATGTTCTTTTAAACGGTAAAAAA

FIGURE 330

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFIADYFETSSQCSK
PSVIFLTKRGRQVCADPSEEWVQKYVSDLELSA

Signal sequence:
1-23

Small cytokines (intercrine/chemokine) C-C subfamily signature:
1-35, 2-36, 10-44, 34-74, 50-90

Small cytokines (intecrine/chemokine):
24-89

FIGURE 331

GGCACGAGGTGAGACTTTAAATGAA**ATG**TCTCACAAGCTAGGTGATCCAGGTTTTGTGGT
CTTTGCAACCCTTGTGGTCATTGTGGCCTTGATATTAATCTTCGTGGTGGGTCCTCGCCA
TGGACAGACAAACATTCTTGTGTACATAACAATCTGCTCTGTAATCGGCGCGTTTTCAGT
CTCCTGTGTGAAGGGCCTGGGCATTGCTATCAAGGAGCTGTTTGCAGGGAAGCCTGTGCT
GCGGCATCCCCTGGCTTGGATTCTGCTGCTGAGCCTCATCGTCTGTGTGAGCACACAGAT
TAATTACCTAAATAGGGCCCTGGATATATTCAACACTTCCATTGTGACTCCAATATATTA
TGTATTCTTTACAACATCAGTTTTAACTTGTTCAGCTATTCTTTTTAAGGAGTGGCAAGA
TATGCCTGTTGACGATGTCATTGGTACTTTGAGTGGCTTCTTTACAATCATTGTGGGGAT
ATTCTTGTTGCATGCCTTTAAAGACGTCAGCTTTAGTCTAGCAAGTCTGCCTGTGTCTTT
TCGAAAAGACGAGAAAGCAATGAATGGCAATCTCTCTAATATGTATGAAGTTCTTAATAA
TAATGAAGAAAGCTTAACCTGTGGAATCGAACAACACACTGGTGAAAATGTCTCCCGAAG
AAATGGAAATCTGACAGCTTTT**TAA**GAAAGGTGTAATTAAAGGTTAATCTGTGATTGTTA
TGAAGTGAATTTGAATATCATCAGAATGTGTCTGAAAAAACATTGTCCTCAAATAATGTT
CTTTAAAGGCAATCTTTTTAAAGATTTCACTAATTTGGACCAAGAAATTACTTTTCTTGT
ATTTAAACAAACAATGGTAGCTCACTAAAATGACCTCAGCACATGACGATTTCTATTAAC
ATTTTATTGTTGTAGAAGTATTTTACATTTTCATCCCTTCTCCAAAAGCCGAATGCACTA
ATGACAGTTTTAAGTCTATGAAAATGCTTTATTTTTTCATTGGTGATGAAAGTCTGAAAT
GTGCATTTGTCATCCCCACTCCATCAATCCCTGACCATGTAAGGCTTTTTTATTTTAAAA
AAACAGAGTTATCCCAATACATTATCCTGTGATTTACCTTACCTACAAAAGTGGCTCCTG
TTTGTTTGATGATGATTGGTTTTATTTTTGAAATATTTATTAAGGGAAAACTAAGTTACT
GAATGAAGGAACCTCTTTCTTACAAAACAAAAAAAAGGGCAGAAATCACCCCAAGGAACG
ATTTCTCAGGTTGAGATGATCACCGTGAATCCGGCTTCCTCTGAGCATTCGATGGCCTTA
GCACCTCATCAAGCCAGCACATCCTGCCTGCTGTTGCAGCCTGGCTGGGTTTATTCTTCA
GTTACCCTAATCCCATGATGCCTGGAACCTTGATTACCGTTTTACATCAGCTCTTGTACT
TTTCAGTATATTTTCATAATGAGTTATATTGTCATTTAGACTTTGAACAGCTCTGGGAAA
TAGAAGACTAGGGTTGTTTCTTAAATTTAGCTCATGTTATAATAAAAAGTTGAAATG

FIGURE 332

MSHKLGDPGFVVFATLVVIVALILIFVVGPRHGQTNILVYITICSVIGAFSVSCVKGLGI
AIKELFAGKPVLRHPLAWILLLSLIVCVSTQINYLNRALDIFNTSIVTPIYYVFFTTSVL
TCSAILFKEWQDMPVDDVIGTLSGFFTIIVGIFLLHAFKDVSFSLASLPVSFRKDEKAMN
GNLSNMYEVLNNNEESLTCGIEQHTGENVSRRNGNLTAF

Signal sequence:
1-33

Transmembrane domain:
40-60, 70-90, 103-123, 139-159

N-glycosylation site:
103-106, 182-185, 208-211, 215-218

N-myristoylation site:
57-62, 140-145, 181-186, 214-219

FIGURE 333

GTG<u>**ATG**</u>GCGGCTGGTGATGGGGACGTGAAGCTAGGCACCCTGGGGAGTGGCAGCGAGAGC
AGCAACGACGGCGGCAGCGAGAGTCCAGGCGACGCGGGAGCGGCAGCGGAAGGGGGAGGC
TGGGCGGCGGCGGCGTTGGCGCTTCTGACGGGGGGCGGGGAAATGCTGCTGAACGTGGCG
CTGGTGGCTCTGGTGCTGCTGGGGGCCTACCGGCTGTGGGTGCGCTGGGGGCGGCGGGGT
CTGGGGGCCGGGGCCGGGGCGGGCGAGGAGAGCCCCGCCACCTCTCTGCCTCGCATGAAG
AAGCGGGACTTCAGCTTGGAGCAGCTGCGCCAGTACGACGGCTCCCGCAACCCGCGCATC
CTGCTCGCGGTCAATGGGAAAGTCTTCGACGTGACCAAAGGCAGCAAGTTCTACGGCCCG
GCGGGTCCATATGGAATATTTGCTGGTAGGGATGCCTCCAGAGGACTGGCCACATTTTGC
CTAGATAAAGATGCACTTAGAGATGAATATGATGATCTCTCAGATTTGAATGCAGTACAA
ATGGAGAGTGTTCGAGAATGGGAAATGCAGTTTAAAGAAAAATATGATTATGTAGGCAGA
CTCCTAAAACCAGGAGAAGAACCATCAGAATATACAGATGAAGAAGATACCAAGGATCAC
AATAAACAGGAT<u>**TGA**</u>ACTTTGTAAACAACCAAAGTCAGGGGCCTTCAGAACTGCAATTCT
TACTCCCTTTCACAGACTGTCCGGAGTCTTTGGGTTTGATTCACCTGCTGCGAAAAACAT
TCAACAAATTGTGTACAAGATAAATTAATCTCACTATGAAGATTTGAATAACTAGACATT
ATTTATGCTGCCAAACTCATTTGTTGCAGTTGTTTGTAATGTCTAGTGGGGCTTCATCAT
CCTGAAAAGAAGGAGACAGGGATTTTTTTAAAGAGCAAGAAAGTCACAATATTACTTCTT
TCCTTCCTTTTTTCCTTCTTTCCTTTCTTCTTTCTCTTTCTTTCTTTTTAAAATATATTG
AAGACAACCAGATATGTATTTGCTACTCAAGTGTACAGATCTCCTCAAGAAACATCAAGG
G

FIGURE 334

MAAGDGDVKLGTLGSGSESSNDGGSESPGDAGAAAEGGGWAAAALALLTGGGEMLLNVAL
VALVLLGAYRLWVRWGRRGLGAGAGAGEESPATSLPRMKKRDFSLEQLRQYDGSRNPRIL
LAVNGKVFDVTKGSKFYGPAGPYGIFAGRDASRGLATFCLDKDALRDEYDDLSDLNAVQM
ESVREWEMQFKEKYDYVGRLLKPGEEPSEYTDEEDTKDHNKQD

Signal sequence:
None

Transmembrane domain:
45-65

Tyrosine kinase phosphorylation site:
202-210

N-myristoylation site:
11-16, 16-21, 37-42, 38-43, 79-84, 81-86, 83-88, 144-149

Amidation site:
75-78

FIGURE 335

GACAGGCCGGGGTTACTGTGGCGACCACGAGAGCAGCTTTGGCGCTATGGAGGAGCCCGG
GGCTACCCCTCAACCGTATTTGGGGCTGCTCCTGGAGGAGCTACGCAGGGTTGTGGCAGC
ACTGCCTGAAGGTATGAGACCAGATTCTAATCTTTATGGTTTTCCATGGGAATTGGTGAT
ATGTGCAGCTGTTGTTGGATTTTTTGCTGTTCTCTTTTTTTTGTGGAGAAGTTTTAGATC
GGTTAGGAGTCGGCTTTATGTGGGACGAGAGAAAAAGCTTGCTCTAATGCTTTCTGGACT
AATTGAAGAAAAAAGTAAACTACTTGAAAAATTTAGCCTTGTTCAAAAAGAGTATGAAGG
CTATGAAGTAGAGTCATCTTTAAAGGATGCCAGCTTTGAGAAGGAGGCAACAGAAGCACA
AAGTTTGGAGGCAACCTGTGAAAAGCTGAACAGGTCCAATTCTGAACTTGAGGATGAAAT
ACTCTGTCTAGAAAAAGAGTTAAAAGAAGAGAAATCCAAACATTCTGAACAAGATGAATT
GATGGCGGATATTTCAAAAAGGATACAGTCTCTAGAAGATGAGTCAAAATCCCTCAAATC
ACAAGTAGCTGAAGCCAAAATGACCTTCCAGATATTTCAAATGAATGAAGAACGACTGAA
GATAGCAATAAAAGATGCTTTGAATGAAAATTCTCAACTTCAGGAAAGCCAGAAACAGCT
TTTGCAAGAAGCTGAAGTATGGAAAGAACAAGTGAGTGAACTTAATAAACAGAAAGTAAC
ATTTGAAGACTCCAAAGTACATGCAGAACAAGTTCTAAATGATAAAGAAAGTCACATCAA
GACTCTGACTGAACGCTTGTTAAAGATGAAAGATTGGGCTGCTATGCTTGGAGAAGACAT
AACGGATGATGATAACTTGGAATTAGAAATGAACAGTGAATCGGAAAATGGTGCTTACTT
AGATAATCCTCCAAAAGGAGCTTTGAAGAAACTGATTCATGCTGCTAAGTTAAATGCTTC
TTTAAAAACCTTAGAAGGAGAAAGAAACCAAATTTATATTCAGTTGTCTGAAGTTGATAA
AACAAAGGAAGAGCTTACAGAGCATATTAAAAATCTTCAGACTCAACAAGCATCTTTGCA
GTCAGAAAACACACATTTTGAAAATGAGAATCAGAAGCTTCAACAGAAACTTAAAGTAAT
GACTGAATTATATCAAGAAAATGAAATGAAACTCCACAGGAAATTAACAGTAGAGGAAAA
TTATCGGTTAGAGAAAGAAGAGAAACTTTCTAAAGTAGATGAAAAGATCAGCCATGCCAC
TGAAGAGCTGGAGACCTATAGAAAGCGAGCCAAAGATCTTGAAGAAGAATTGGAGAGAAC
TATTCATTCTTATCAAGGGCAGATTATTTCCCATGAGAAAAAAGCACATGATAATTGGTT
GGCAGCTCGGAATGCTGAAAGAAACCTCAATGATTTAAGGAAAGAAAATGCTCACAACAG
ACAAAAATTAACTGAAACAGAGCTTAAATTTGAACTTTTAGAAAAAGATCCTTATGCACT
CGATGTTCCAAATACAGCATTTGGCAGAGGCTCACGAGGCCCAGGGAATCCTCTGGACCA
TCAGATTACCAATGAAAGAGGAGAATCAAGCTGTGATAGGTTAACCGATCCTCATAGGGC
TCCCTCTGACACTGGGTCTCTGTCACCTCCATGGGACCAGGACCGTAGGATGATGTTTCC
TCCGCCAGGACAATCATATCCTGATTCAGCCCTTCCTCCACAAAGGCAAGACAGATTTTG
TTCTAATTCTGGTAGACTGTCTGGACCAGCAGAACTCAGAAGTTTTAATATGCCTTCTTT
GGATAAAATGGATGGGTCAATGCCTTCAGAAATGGAATCCAGTAGAAATGATACCAAAGA
TGATCTTGGTAATTTAAATGTGCCTGATTCATCTCTCCCTGCTGAAAATGAAGCCACTGG
CCCTGGCTTTGTTCCTCCACCTCTTGCTCCAATCAGAGGTCCATTGTTTCCAGTGGATGC
AAGAGGCCCATTCTTGAGAAGAGGACCTCCTTTCCCCCCACCTCCTCCAGGAGCCATGTT
TGGAGCTTCTCGAGATTATTTTCCACCAAGGGATTTCCCAGGTCCACCACCTGCTCCATT
TGCAATGAGAAATGTCTATCCACCGAGGGGTTTTCCTCCTTACCTTCCCCCAAGACCTGG
ATTTTTCCCCCCACCCCCACATTCTGAAGGTAGAAGTGAGTTCCCCTCAGGTTTGATTCC
ACCTTCAAATGAGCCTGCTACTGAACATCCAGAACCACAGCAAGAAACC<u>TGA</u>CAATATTT
TTGCTCTCTTCAAAAGTAATTTTGACTGATCTCATTTTCAGTTTAAGTAACTGCTGTTAC
TTAAGTGATTACACTTTTGCTCAAATTGAAGCTTAATGGAATTATAATTCTCAGGATAGT
ATTTTGTAAATAAAGATGATTTAAATATGAATCTTATGAGTAAATTATTTCAATTTTATT
TTAGACGGTATAACTATTTCAATTTGATTAATCCACTATTATATAAACAATAGTGGGAGT
TTTATATATGTAATCTTTCAGGTGGGGAGGCTTTAAATTCTGAAGTCTGTGTCTTTATGC
CAAGAACTGTATTTACTGTGGTTGTGGACAAATGTGAAAGTAACTTTATGCTTAAATAAA
TTATAGTTGATTTAAAGATTTGTTTGGCATTGATAATAATAAAATCAGTAGTTTTTCTAT
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 336

TGRGYCGDHESSFGAMEEPGATPQPYLGLLLEELRRVVAALPEGMRPDSNLYGFPWELVI
CAAVVGFFAVLFFLWRSFRSVRSRLYVGREKKLALMLSGLIEEKSKLLEKFSLVQKEYEG
YEVESSLKDASFEKEATEAQSLEATCEKLNRSNSELEDEILCLEKELKEEKSKHSEQDEL
MADISKRIQSLEDESKSLKSQVAEAKMTFQIFQMNEERLKIAIKDALNENSQLQESQKQL
LQEAEVWKEQVSELNKQKVTFEDSKVHAEQVLNDKESHIKTLTERLLKMKDWAAMLGEDI
TDDDNLELEMNSESENGAYLDNPPKGALKKLIHAAKLNASLKTLEGERNQIYIQLSEVDK
TKEELTEHIKNLQTQQASLQSENTHFENENQKLQQKLKVMTELYQENEMKLHRKLTVEEN
YRLEKEEKLSKVDEKISHATEELETYRKRAKDLEEELERTIHSYQGQIISHEKKAHDNWL
AARNAERNLNDLRKENAHNRQKLTETELKFELLEKDPYALDVPNTAFGRGSRGPGNPLDH
QITNERGESSCDRLTDPHRAPSDTGSLSPPWDQDRRMMFPPPGQSYPDSALPPQRQDRFC
SNSGRLSGPAELRSFNMPSLDKMDGSMPSEMESSRNDTKDDLGNLNVPDSSLPAENEATG
PGFVPPPLAPIRGPLFPVDARGPFLRRGPPFPPPPPGAMFGASRDYFPPRDFPGPPPAPF
AMRNVYPPRGFPPYLPPRPGFFPPPPHSEGRSEFPSGLIPPSNEPATEHPEPQQET

Signal sequence:
None

Transmembrane domain:
54-74

N-glycosylation site:
150-153, 338-341, 636-639

cAMP- and cGMP-dependent protein kinase phosphorylation site:
413-416

Tyrosine kinase phosphorylation site:
414-421

N-myristoylation site:
466-417, 625-630, 697-702

Leucine zipper pattern:
142-163

FIGURE 337

GGACTGCGGTCTCGGGCAGCA**ATG**GCCGAGAAGCGCGACACACGGGACTCCGAAGCCCAG
CGGCTCCCCGACTCCTTCAAGGACAGCCCCAGTAAGGGCCTTGGACCTTGCGGATGGATT
TTGGTGGCGTTCTCATTCTTATTCACCGTTATAACTTTCCCAATCTCAATATGGATGTGC
ATAAAGATTATAAAAGAGTATGAAAGAGCCATCATCTTTAGATTGGGTCGCATTTTACAA
GGAGGAGCCAAAGGACCTGGTTTGTTTTTATTCTGCCATGCACTGACAGCTTCATCAAA
GTGGACATGAGAACTATTTCATTTGATATTCCTCCTCAGGAGATCCTGACAAAGGATTCA
GTGACAATTAGCGTGGATGGTGTGGTCTATTACCGCGTTCAGAATGCAACCCTGGCTGTG
GCAAATATCACCAACGCTGACTCAGCAACCCGTCTTTTGGCACAAACTACTCTGAGGAAT
GTTCTGGGCACCAAGAATCTTTCTCAGATCCTCTCTGACAGAGAAGAAATTGCACACAAC
ATGCAGTCTACTCTGGATGATGCCACTGATGCCTGGGGAATAAAGGTGGAGCGTGTGGAA
ATTAAGGATGTGAAACTACCTGTGCAGCTCCAGAGAGCTATGGCTGCAGAAGCAGAAGCG
TCCCGCGAGGCCCGCGCCAAGGTTATTGCAGCCGAAGGAGAAATGAATGCATCCAGGGCT
CTGAAAGAAGCCTCCATGGTCATCACTGAATCTCCTGCAGCCCTTCAGCTCCGATACCTG
CAGACACTGACCACCATTGCTGCTGAGAAAAACTCAACAATTGTCTTCCCTCTGCCCATA
GATATGCTGCAAGGAATCATAGGGGCAAAACACAGCCATCTAGGC**TAG**TGTAGAGATGAG
CGCTAGCCTTCCAAGCATGAAGTCGGGGACCAAATTAGCCTTTAACTCATAAAGAGAGGG
TAGGGCTTTTCTTTTTCCATATGTCAATTGTGGTGTTCCCAGAATGTATAGCAGTTATAA
AAATAGGTGAAAGAATTGTTAGCTTGTAAATACTGAGAGATTGGTGATTTATATAAGGTA
ATCTGTTAGTCTTAAAATAGTTAAAAGTTTGTATTTTTAGATTATTATGTAGTAGGTTAG
ATCCCTCTTGTTTTGACTTCCACTGACTCATTCTGAACCCCCTAAGCACCCAGGCCACAG
GCAAGAACCTGGGCTGTAACTGCCACCTGACACCGCTGACTGGCTAAATGCTTTGCAGAA
AGTGATGACCTTACACCACAACCAGCTTCTCCAGGTCATATGTGCCTTACCTCCAGAAGT
CTTTTTTTTTTTTTTTTTCTGAGATGGAGTTTCACTCTTGTTGCCCAGGCTGGAGTGCAA
TAGCATGATCTCGGCTCACTGCAACCTCCGCCTCCTGGGTTCAAGAGATTCTCCTGCCTC
AGCCTCCCCAGTAGCTGGGATTACAGGCTCATGCCACCATGCCCAGCTAATTTTTGTATT
ATTATTATTGTTTTTTAGTAGAGACGGGGTTTCACCATGTTGGCCAGGCTAGTCACGAAC
TCCTAACCTCAGGTGATCCACCCACCTCTGCCTCCAAAGTGCTGGATTACAGGCTGAGCT
ACCACCCTGGTTTGGAGAGTCTTAATTAATTGAAATTTCCCTAATGTTCATTTATTTTCT
AAATCCAGCCGTGTTTCAGAATAATCCTTACTTGAGAGTAGCCATTTTCTTGTGTACTTG
TCAGAACTAGAGGAAATAGCCAAGACTAATGAAAAACATTACTCTAACCCTTAAAAGACT
TTTAAATTCACTACTAGAGTGGTCATTTTAAAAATACATCCATGTTTTAACTTATTTTGA
GCCTTTCTTTTATGAGTAAATGATTCCTCCTTGTTCTGTCTTTCAAACCAGCTAAATATT
TGTCACAAAAGTGACTTTTTTCTCACTGTTGCCTATTTTCATATATCAGGTTTTAAATAG
TTTTAATTTTTTAATAAAATTTTTCTCTACGTTCTATATGCAATTGTTATATATCTATTT
GAATAGCTGAAGGACTAAAATACTTTTTTAAGAGATAACTTCAGGAAACCATTATATTTT
ACTATCTGCATGCTGTTAACTGTGGTACACTGTGAAATATGTTGATTACAAACCCATTCA
TTACATAGTATAAGGAATTCACAGTATATTGACTATATAGTGTCTAATGACTGGGCAGAT
ACTGTCAACTTACAATATCTATATAGAGAGGCTTTAAACTTACCTTACTCATTCTCTATG
ATGTATGACTTGATGCTGAAAGAGGAAGCTGGTCAGCTCCTCATGGACAACAAATTCTTA
GTCTATAATATTAGGAGACATCTCTAGTTTTGCAAATGTCTGTGAATCTGAGCAACCTGG
ACTTCTGCTTACTGGCCAGAAAGCTGGCGGGTGACATTTGTAACATTTCCTCTTTGAGAC
TCTGAGTTCACCTAGAGAAGTCTAAGCATAACAGCTTTCTTTCCCAGCACGAGCCTTTAT
AGCTCTCTTTAGCTCAACCACTCTGTCCATCCAGCCAATGGATGTCCTTCCCTGTACCCA
ATTCAAGCTTATTTTAGGGAAGCCTTGAAACTACCATGTATCTGGCTCTAGCTGAGTTAT
TGAGGATTGAGCCAGTGCAACGTTAAACTCAGTGCACTTACATTTGATTTAAATGATGGT
TTTATCTGTTGTGTGAAGTGGTTCACCCTTGAGGACCAGGAGCCTCCATATCCTGACTGA
AAACCTTTTCTGAGACTTAGAGTAACAGTACTTTTGGTTCCTTGAGTTCTCCTGTCTCCA
GATACCTAAATGACCTTGACTTTTCTGCCTTGTGAATTCGTAGTCCAATCAGCTGAAATT
AAATCACTTGGGAGGGACGCATAGAAGGAGCTCTAGGAACACAGTGCCAGTGCAGAAGTT
TCTCCAGGTGGCCTCCCTTTCCAACAATGTACATAATAAAGTGTATGCACTTTCACT

FIGURE 338

MAEKRDTRDSEAQRLPDSFKDSPSKGLGPCGWILVAFSFLFTVITFPISIWMCIKIIKEY
ERAIIFRLGRILQGGAKGPGLFFILPCTDSFIKVDMRTISFDIPPQEILTKDSVTISVDG
VVYYRVQNATLAVANITNADSATRLLAQTTLRNVLGTKNLSQILSDREEIAHNMQSTLDD
ATDAWGIKVERVEIKDVKLPVQLQRAMAAEAEASREARAKVIAAEGEMNASRALKEASMV
ITESPAALQLRYLQTLTTIAAEKNSTIVFPLPIDMLQGIIGAKHSHLG

Signal sequence:
1-45

Transmembrane domain:
None

N-glycosylation site:
128-131, 135-138, 159-162, 229-232, 264-267

cAMP- and cGMP-dependent protein kinase phosphorylation site:
4-7

N-myristoylation site:
26-31, 278-283, 281-286

SPFH domain/Band 7 family:
39-230

FIGURE 339

TCTAGAGCCCTCTCCCAAC**ATG**GCGGCCTCAGCAAAAAAGAAGAATAAGAAGGGGAAGAC
TATCTCCCTAACAGACTTTCTGGCTGAGGATGGGGGTACTGGTGGAGGAAGCACCTATGT
TTCCAAACCAGTCAGCTGGGCTGATGAAACGGATGACCTGGAAGGAGATGTTTCGACCAC
TTGGCACAGTAACGATGACGATGTGTATAGGGCGCCTCCAATTGACCGTTCCATCCTTCC
CACTGCTCCACGGGCTGCTCGGGAACCCAATATCGACCGGAGCCGTCTTCCCAAATCGCC
ACCCTACACTGCTTTTCTAGGAAACCTACCCTATGATGTTACAGAAGAGTCAATTAAGGA
ATTCTTTCGAGGATTAAATATCAGTGCAGTGCGTTTACCACGTGAACCCAGCAATCCAGA
GAGGTTGAAAGGTTTTGGTTATGCTGAATTTGAGGACCTGGATTCCCTGCTCAGTGCCCT
GAGTCTCAATGAAGAGTCTCTAGGTAACAGGAGAATTCGAGTGGACGTTGCTGATCAAGC
ACAGGATAAAGACAGGGATGATCGTTCTTTTGGCCGTGATAGAAATCGGGATTCTGACAA
AACAGATACAGACTGGAGGGCTCGTCCTGCTACAGACAGCTTTGATGACTACCCACCTAG
AAGAGGTGATGATAGCTTTGGAGACAAGTATCGAGATCGTTATGATTCAGACCGGTATCG
GGATGGGTATCGGGATGGGTATCGGGATGGCCCACGCCGGGATATGGATCGATATGGTGG
CCGGGATCGCTATGATGACCGAGGCAGCAGAGACTATGATAGAGGCTATGATTCCCGGAT
AGGCAGTGGCAGAAGAGCATTTGGCAGTGGGTATCGCAGGGATGATGACTACAGAGGAGG
CGGGGACCGCTATGAAGACCGATATGACAGACGGGATGATCGGTCGTGGAGCTCCAGAGA
TGATTACTCTCGGGATGATTATAGGCGTGATGATAGAGGTCCCCCCCAAAGACCCAAACT
GAATCTAAAGCCTCGGAGTACTCCTGAAGAAGATGATTCCTCTGCTAGTACCTCCCAGTC
CACTCGAGCTGCTTCTATCTTTGGAGGGGCAAAGCCTGTTGACACAGCTGCTAGAGAAAG
AGAAGTAGAAGAACGGCTACAGAAGGAACAAGAGAAGTTGCAGCGTCAGTGGAATGAGCC
AAAACTAGAACGACGGCCTCGGGAGAGACACCCAAGCTGGCGAAGTGAAGAAACTCAGGA
ACGGGAACGGTCGAGGACAGGAAGTGAGTCATCACAAACTGGGACCTCCACCACATCTAG
CAGAAATGCACGAAGGAGAGAGAGAGTGAGAAGTCTCTAGAAAATGAAACACTCAATAAGGA
GGAAGATTGCCACTCTCCAACTTCTAAACCTCCCAAACCTGATCAGCCCCTAAAGGTAAT
GCCAGCCCCTCCACCAAAGGAGAATGCTTGGGTGAAGCGAAGTTCTAACCCTCCTGCTCG
ATCTCAGAGCTCAGACACAGAGCAGCAGTCCCCTACAAGTGGTGGGGGAAAAGTAGCTCC
AGCTCAACCATCTGAGGAAGGACCAGGAAGGAAAGATGAAAATAAAGTAGATGGGATGAA
TGCCCCAAAAGGCCAAACTGGGAACTCTAGCCGTGGTCCAGGAGACGGAGGGAACAGAGA
CCACTGGAAGGAGTCAGATAGGAAAGATGGCAAAAAGGATCAAGACTCCAGATCTGCACC
TGAGCCAAAGAAACCTGAGGAAAATCCAGCTTCTAAGTTCAGTTCTGCAAGCAAGTATGC
TGCTCTCTCTGTTGATGGTGAAGATGAAAATGAGGGAGAAGATTATGCCGAA**TAG**ACCTC
TACATCCTGTGCTTTTCTCCTAGTTTCTCTCCACCCTGGAACATTCGAGAGCAAATCAAA
ACCTCTATCCAGACAAGACAAAATAAAACTCAACATCTCCTGAAGACCTTTCTTACCTTT
TTTTAAAAACAAAAAXTGAAATTATTTGCATGCTGCTGCAGCCTTTAAAGTATTGAAGT
AACTGGAGAATTGCCAATACAGCCAGAGAGAAAGGGACTACAGCTTTTTAGAGGAAAAGT
TGTGGTGCGTTATGTCACCATGCAGTTGCCAGTGTGATTAGTGCCTAGGGGTCTCATTTA
GCAGAAATGGTAATGACAGTGATATAATGCCTGGAACCTGGTTGGGCAGTAGGGGAGGGA
GGTAGAAGGAAAAGTGTGAGATTTCTACCTTTTAGTTTTCATCCTATTGTGGCATATATG
AATTCTCAAACATTATCTGAATAAATTTTCCACTCTTGGAAAGGTAGATTTAGCCTCAAG
TTGTTCTAGTCTCCAGGAGGCTGCCAGCCCCTCCTCTTATTTAATTCTGAGTTTTGGGGG
CCAGCCTAGAGGGAATTCCTTTTTTTTTTTTTTTAACCCCCCAGGGGGGTAGTTGGGAGT
GAGACTATAGGCCATAAAGAATGGGACTGCATTGGACCAAAATAAATGGGAAAATCGTGG
TTTGAAAAGAAGCTTTTGGGAAGTGATGAGTCATTTTGCACCAGGTAATAGGGGAAAATT
GTGTGACCTCCAGCAAACACATGAATGGTTATTTCCTGGAGCCGGAAGCACTTGGGGGTC
GTGGTAATTCCCAGTGTTTTCTGTGTCCTAGTTTTACCCTTTCTAAACACTGTCCTTTTT
GAAAGTTTTGAATATATCCACATTCTATTGAAACCTTGAAACTAAAAATTTAGACTCTTA
TCGTCATCTTAAGTTCTTCATGCTACTCTTAACCTCCCAAAAAGCAGTATCTAAGTCACA
TACATGATGTCTTGGGCATTTTCTGAGCCATGGAGAACTCTGAAAGGAAGAATCGCTGCT
TTTCTCAAGCAAATCGGTTTCTTGATGTCTTTTGGTTCTCCTTGCCTGCTCCTGATGCTT

GGACCCCTTTTATTGATCAGAGTGCTCTAGAATAATGGATGGTCTTGGATGATGGATAAA
TAGGGACAGGGACAGTTAAATTGGGAGCCTTTCTTACAACCTTGATGGGATTTTTCCCCC
CAAGTTTCCTTCTCCACTGAAATGCCACACTAATGCTTGTTGGATTCATGAGGTGGCCAG
ACCAATGTGTTGTTTTGTTGTTGTTTTTTTTTTAAGCTTCCCTTGAGAGAATAAATGGTA
ATGGAGAGAATCATTTAACAAGGTCCTGGTTTCTCTTGCAACACAGTAGCTAAACTTGCC
TGCTTTTATATGCATTTTTGTAGGGATCAGCTTGGTAGACAGTATTAGCGGAGAAACACC
TTGATCTTGGTTTGCAAGCCCTTCTCCCATCAGTCCTAGATTAGGCCCTGTTCAGCCATG
CAGGGGTGTTGGTTTATGCGTGCTGCAGCAGTGGGCATAATGAATATAATTTACCCAGTG
GACAAAGGTGTGTACCAAGTGAATTTAAATAATTGGTGTGGATTGGCCAGTAGCTAAGAA
GTGGGCTTTTAAAGAGTATTGAAGATTGAAAGGGTTTTTCTTTCTTTTTTAAAAAAGAAA
AACAAACTATTGATTGTAGATAATGAAAAGCTAGGGTTTGCCCTCTTCATGTCTACTCTC
CTTCCAAATAGTTATATCCAAAACTGTTTTTCCCTCTCCCCTACCTTGTCCCCCCTATTA
AAATAGAAACAGGGATTGATTAATGTCCCGCTCCTGAATACATGTAAAATTTGTACAAAA
ATATCTTCTATGAAAATGATTTGTAATCTGTAGACTTATTACCTGGGAGATGTCTTGATG
TAAAATCCCATCCTTTGGGTTGTGGGTTTTTTGTTTTCTCCAAATAAATCTGATCTTTAA
AGTTAAAAAAAAAAAAAAAACTCTAGAGTCGAGGAATTC

FIGURE 340

MAASAKKKNKKGKTISLTDFLAEDGGTGGGSTYVSKPVSWADETDDLEGDVSTTWHSNDD
DVYRAPPIDRSILPTAPRAAREPNIDRSRLPKSPPYTAFLGNLPYDVTEESIKEFFRGLN
ISAVRLPREPSNPERLKGFGYAEFEDLDSLLSALSLNEESLGNRRIRVDVADQAQDKDRD
DRSFGRDRNRDSDKTDTDWRARPATDSFDDYPPRRGDDSFGDKYRDRYDSDRYRDGYRDG
YRDGPRRDMDRYGGRDRYDDRGSRDYDRGYDSRIGSGRRAFGSGYRRDDDYRGGGDRYED
RYDRRDDRSWSSRDDYSRDDYRRDDRGPPQRPKLNLKPRSTPEEDDSSASTSQSTRAASI
FGGAKPVDTAAREREVEERLQKEQEKLQRQWNEPKLERRPRERHPSWRSEETQERERSRT
GSESSQTGTSTTSSRNARRRESEKSLENETLNKEEDCHSPTSKPPKPDQPLKVMPAPPPK
ENAWVKRSSNPPARSQSSDTEQQSPTSGGGKVAPAQPSEEGPGRKDENKVDGMNAPKGQT
GNSSRGPGDGGNRDHWKESDRKDGKKDQDSRSAPEPKKPEENPASKFSSASKYAALSVDG
EDENEGEDYAE

Signal Sequence:
None

Transmembrane domain:
None

N-glycosylation site:
120-123, 448-451, 542-545

Glycosaminoglycan attachment site:
507-510

cAMP- and cGMP-dependent protein kinase phosphorylation site:
439-442, 486-489

Tyrosine kinase phosphorylation site:
225-233, 264-270

N-myristoylation site:
25-30, 26-31, 28-33, 118-123, 421-426, 428-433, 538-543

Amidation site:
276-279, 522-525, 563-566

Cell attachment sequence:
215-217

Eukaryotic putative RNA-binding region RNP-1 signature:
137-144

RNA recognition motif:
98-168

FIGURE 341

GCGTGGACACCACCTCAGCCCACTGAGCAGGAGTCACAGCACGAAGACCAAGCGCAAAGC
GACCCCTGCCCTCCATCCTGACTGCTCCTCCTAAGAGAG<u>ATG</u>GCACCGGCCAGAGCAGGA
TTCTGCCCCCTTCTGCTGCTTCTGCTGCTGGGGCTGTGGGTGGCAGAGATCCCAGTCAGT
GCCAAGCCCAAGGGCATGACCTCATCACAGTGGTTTAAAATTCAGCACATGCAGCCCAGC
CCTCAAGCATGCAACTCAGCCATGAAAAACATTAACAAGCACACAAAACGGTGCAAAGAC
CTCAACACCTTCCTGCACGAGCCTTTCTCCAGTGTGGCCGCCACCTGCCAGACCCCCAAA
ATAGCCTGCAAGAATGGCGATAAAAACTGCCACCAGAGCCACGGGCCCGTGTCCCTGACC
ATGTGTAAGCTCACCTCAGGGAAGTATCCGAACTGCAGGTACAAAGAGAAGCGACAGAAC
AAGTCTTACGTAGTGGCCTGTAAGCCTCCCCAGAAAAAGGACTCTCAGCAATTCCACCTG
GTTCCTGTACACTTGGACAGAGTCCTT**<u>TAG</u>**GTTTCCAGACTGGCTTGCTCTTTGGCTGAC
CTTCAATTCCCTCTCCAGGACTCCGCACCACTCCCCTACACCCAGAGCATTCTCTTCCCC
TCATCTCTTGGGGCTGTTCCTGGTTCAGCCTCTGCTGGGAGGCTGAAGCTGACACTCTGG
TGAGCTGAGCTCTAGAGGGATGGCTTTTCATCTTTTTGTTGCTGTTTTCCCAGATGCTTA
TCCCCAAGAAACAGCAAGCTCAGGTCTGTGGGTTCCCTGGTCTATGCCATTGCACATGTC
TCCCCTGCCCCCTGGCATTAGGGCAGCATGACAAGGAGAGGAAATAAATGGAAAGGGGGC
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 342

MAPARAGFCPLLLLLLLGLWVAEIPVSAKPKGMTSSQWFKIQHMQPSPQACNSAMKNINK
HTKRCKDLNTFLHEPFSSVAATCQTPKIACKNGDKNCHQSHGPVSLTMCKLTSGKYPNCR
YKEKRQNKSYVVACKPPQKKDSQQFHLVPVHLDRVL

Important features of the protein

Signal peptide:
1-22

Transmembrane domain:
none

N-glycosylation site:
127-131

cAMP- and cGMP-dependent protein kinase phosphorylation site:
139-143

N-myristoylation site:
18-24, 32-38

Pancreatic ribonuclease family signature:
65-72

Pancreatic ribonuclease family proteins:
49-93

FIGURE 343

GCATTTGCCACTGGTTGCAGATCAGGCGGACGAGGAGCCGGGAAGGCAGAGCC<u>ATG</u>TGGC
TGCCCCCTGCTCTGCTCCTTCTCAGCCTCTCAGGCTGTTTCTCCATCCAAGGCCCAGAGT
CTGTGAGAGCCCCAGAGCAGGGGTCCCTGACGGTTCAATGCCACTATAAGCAAGGATGGG
AGACCTACATTAAGTGGTGGTGCCGAGGGGTGCGCTGGGATACATGCAAGATCCTCATTG
AAACCAGAGGGTCGGAGCAAGGAGAGAAGAGTGACCGTGTGTCCATCAAGGACAATCAGA
AAGACCGCACGTTCACTGTGACCATGGAGGGGCTCAGGCGAGATGACGCAGATGTTTACT
GGTGTGGGATTGAAAGAAGAGGACCTGACCTTGGGACTCAAGTGAAAGTGATCGTTGACC
CAGAGGGAGCGGCTTCCACAACAGCAAGCTCACCTACCAACAGCAATATGGCAGTGTTCA
TCGGCTCCCACAAGAGGAACCACTACATGCTCCTGGTATTTGTGAAGGTGCCCATCTTGC
TCATCTTGGTCACTGCCATCCTCTGGTTGAAGGGGTCTCAGAGGGTCCCTGAGGAGCCAG
GGGAACAGCCTATCTACATGAACTTCTCCGAACCTCTGACTAAAGACATGGCCACT<u>TAG</u>A
GAGATGGATCTGCAGAGCCTTCCTGCCCTGGCCACGTTTCCAGAAGAGACTCGGGCTGTG
GAAGGAACATCTACGAGTCCTCGGGATGCAGTGACTGAGATAGGGGCCCTGGGCCTCCGC
CCTGGCCTTGGAGCTGGTGGGCACCTCCCTGTTCTGCACAGCTCAGGGACTTAGCCAGGT
CCTCTCCTGAGCCACCATCACCTCCTGGGGTGCCAGCACCTGTTCTCTTGGTCAGGAGCT
GTAGAGATGGAGCTCAAGCACTGGACGACTCTGTCCCCACTGCTGGAATAACTCGGGCAC
AGAGCATGGGACCAAAGTACAGAAAGAGGTTGGGGGAGACCCCCCCAGCCCTAGACTTCC
ATCATTCCGGAGACCAACTCAACACCGTCTTTGCCTGAGAACCTGATATATCCGTGTTTT
TAAATTTTTTTTTTTCTAGCAAAGTTGGGTTTAATGACTTATGTTCATAGGAAACCTCT
CTGATCCCACACACAAGGAGGGTGATTCTGGGATGAGTTCCTGGTTCTAGGGCATGAGGG
GCTGGATGGACCCTGTCCCCAGGGAGGACATGGCTCTGAGTCCACAGGGCTGAGGAGGCA
ATGGGAACCTCCCTGGCCCGGCCCGGTGCTTGTCCTCCCCCTCCCACCTCTTCCTCCTCC
TAGCTCCCCAAGCTCCCTGCCTATTCCCCCACCTCCGAGGGGCTGCAGCTTGGGAGCCTC
CTCAGCATGACAGCTTGGGTCTCCTCCCCAAAAGAGCCTGTCAGGCCTCAAGAACCACCT
CCAGGTGGGGAGGGCAGTAACGAAAACCATCGCAGGAAATGGCACCCTCCCTTTTCGGTG
ATGTTGAAATCATGTTACTAATGAAAACTGTCCTAGGGAAGTGGTTCTGTCTCCTCACAG
GCTTCACCCACGGCGATGAGGCCCTTGAATGTGGTCACTTTGTGCTGTATGGTTGAGGGA
CCCTCACACCAAAGGGACCTTCCCATGTGAGATGTGCTCCCGCCCCCACCTGCCCACAAG
CAAACACACCACACATGTTCGGCATGTTGCCCTTTGAACACCCATGAGGACGCCTCCAAC
CTGCTCTTGGTTCTAATAGGGAGTACTGACTGTCAGCAGTGGATAAAGGAGAGGGGACCC
TCTGGTCCCTAGCATGGCACCCAGAGCCTCCCCTCTTCTTGTCCTTCAGCCAAAGAGAAA
CTTTCTCTGACTTTGAACTGAATTTAGGTCTCTGGCCAATGATGGGCCTGAAAATTCCAT
AATGGCCAGAGAGGAGAGTTCGAGCCCGGCTAAGATCCCCTGAGTCATTCTGTGAGGGAC
CAAGACCCACAGTCCACCAGCCCCAGGGCCCTACCTCCTGGAATGCTTTCCTGGATCCAG
CTTCCCGAAGATCCGACCAGACCCAGGGAGGACGGCACCGCTCCGCGGGAGGGAAAGCCA
AAGCATGGTGCTTCACCAGCTGGACTCAGGGGCGAGGGGACATGGGCGCTTGTCAACGTG
ATGTCATTCTTTTCCCACCGTTTCTTCCTGTTGATATTCAATGAATCCGTCAATCTCTCT
GGGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

FIGURE 344

MWLPPALLLLSLSGCFSIQGPESVRAPEQGSLTVQCHYKQGWETYIKWWCRGVRWDTCKI
LIETRGSEQGEKSDRVSIKDNQKDRTFTVTMEGLRRDDADVYWCGIERRGPDLGTQVKVI
VDPEGAASTTASSPTNSNMAVFIGSHKRNHYMLLVFVKVPILLILVTAILWLKGSQRVPE
EPGEQPIYMNFSEPLTKDMAT

Important features of the protein:
Signal peptide:
Amino acids 1-17

Transmembrane domain:
Amino acids 151-170

N-glycosylation site:
Amino acids 190-194

Tyrosine kinase phosphorylation site:
Amino acids 95-103

N-myristoylation sites:
Amino acids 66-72;125-131

Prokaryotic membrane lipoprotein lipid attachment site:
Amino acids 5-16

FIGURE 345

CTGAGCTCCCGGGCTCCGGCAGCGCGCTGGCGGGGCGCCGCATTGCACACTCTGGGGGCG
CCGCAGTGTTCGTGGGATGGGCAGCGGGCTGCAGCTGGCGGCCGGAATCCGCGCGCAGC
CCGGGTGCAAGTTCTCTCCTGTTGCCCTGAGTGCCCACTCCCAGGCCCTCTGTATGAGTG
ACACTTCAGTCTGCC<u>ATG</u>GAACCTGGCCCTGCTCTGGCCTGGCTCCTGCTCCTGAGCCTG
CTGGCGGATTGTCTGAAAGCTGCTCAGTCCCGAGACTTCACAGTGAAAGACATTATCTAC
CTCCATCCTTCAACCACACCATATCCTGGTGGATTTAAATGTTTCACCTGTGAAAAGGCA
GCAGACAATTATGAGTGCAACCGATGGGCTCCAGACATCTACTGCCCTCGAGAGACCAGA
TACTGCTACACTCAGCACACAATGGAAGTCACAGGAAACAGTATCTCAGTCACCAAACGC
TGTGTCCCACTGGAAGAGTGCTTATCCACTGGCTGCAGAGACTCCGAGCATGAAGGCCAC
AAGGTCTGCACTTCTTGTTGTGAAGGAAATATCTGTAACTTGCCACTGCCCCGAAATGAA
ACTGATGCCACATTTGCCACGACGTCACCTATAAATCAGACAAATGGGCACCCACGCTGT
ATGTCAGTGATAGTGTCCTGCTTGTGGTTGTGGTTAGGGCTCATGTTA<u>TAG</u>TGGCTCAGT
GGCTCCATGTGTTAATAGCGATCCATGGGGATCTCGATGGTCCACAGACCTGCATGAGTC
ATTGGCCTGACAGTAATTACACATGTGAGACACAACACTCTTGGAGGTCATCACAGCCAA
GCATTGCCACTTACCATGAGGAATAAATGTTGCTTCATTGTAGCCATTTTGAGTCTAACC
GAGACTCATCAAAGCCTTCTGTCAGTACAGCCCAAGTTCCATACCATAAACGTTTGTTTT
CATTCCAAGAAGTAGTTCTGCATTTATCGAGATCTGGGGTTCTTAATTTGGAAGAATACA
TGCATGAGATGCAGTAGGTCCTGAGACTGTAAGATATTAGGAGTATGTTATAGGGGCATG
TATAGATGTGGGCTTTTCAGGAGAAAAGTAACCATTGGTTTAAATATAATCATGAGTTCA
TTTGTAGCTTTAGAATTTTAAAACATTGACTCCAAACTGAATGGACTATTTCCTTGGAAA
TTCTGACTGAGTCCCTGGAAGAGTAGTAATTCCAACAATTCCAGCCATTTGTTCAATTAA
TTTTCCCAACATTCTTCTCCCAGTGCTGGGAATCACATTTCCTCTGTTCTGTGCAGAAGA
CAAAAAGGCAATCATAAAAGTTTGTTATATTTGTGGGGGTGCCTGGAGGAGGATTTTCCT
CAACTTAATGGAGCCACTGTCCATAAAGTGGCTGTTATCCCTTCATATAATTGGTGAGAT
CAGCCTTCTCCTTGACTTGGCACCTAATTATGCTTCATGAGATCCTAGATTCCACCTGAG
TCAATTGTGTCCAGAGCCCCAAACCAGGATGGAGTTGTTTTCCCCAGATATGGGGTTCTA
TTCAGCCATAGATAATCTAGACAGAGGATTTCAGAATGAAAGGAAAAATGTGTGGAGATT
AGTCCTAGTTCATTCTGAGGGCCGACTAAGTGGCTCAGCCAGCTTCTTACTCCATCTGCA
GTTCATACTGCCAAAGAGCTCCCACTTCCAAATCCCCAGTGACTTTATGGAGAAGATTCT
GCATTAAATTGTCTTTCGAATGATGGGGAAGCAAGGCATAATATGCGATGATGAGGAGAA
AGTAGACCAGTGAGGTGATTGCAAGACTAACAAGGAGACTCAATGGGAAGTTTTTCTTTC
TTTTAGATATTGCTTTTGAAGTAGATGGTAAAATTTTTGTCATCCTTCTTGTATTTTTTG
TACCCCAAGTTACAATTTTTCTTCTTCCTTGTAAATAATTTAAACAGTATTTATTTTTGT
AAGGCATAACTAGAAACTAAAATATATTCTAAAAAATTCATTATTCTGAACAAAGTGATC
AAATTAGAATACATATTTTTCAACAGTGGTAGAGCTTTTAATATATGTTTATTGAAAGTT
ATCTATAATACTTGCACCAGTGTTGAAAAAAGTTAACATGTAGGCAAGAGCAATATGTTT
GTCTCAAGGATTTTTCCATGGTTTCCTCAGTGATGGTGTCCTGGAATTATTCAGGTGGTG
ACCATCACTGGTCTAAGTTTGTGTGCAGGGTTTTCAGACGTGTTTTTGTGAAACTTGGTA
GAACCATGGCTAATAAAGAGGACAGTGTTGTCAGGGTCCATCTGCCCTCCATAGAAAAAT
GTCTCTGGCTCATAAAATGAGACTCCCTCAGGGACTAAATATGAACTGACAGCAGTAACT
CTGATACAGAATAATCTAAATTGCATCAAATGGCCTTAATTCAGAGTTTGTTAGGCTTAT
CAGTATGTTGCTTTTAATTGGGGTGGGAAAGTAGAGGGAGAGAAAGCAAGACATTTATTA
AGCACCTCGTATGTGCCAGGCACTATGCTAAGCACTTTACATAAGTTAGGATTAATCCCT
GCAAGAATCCTATAAAGAATGTTACTAGCATTTACACTTCCCAAATGAAGGTACCAAAGC
TCAAACGCAATGTTGTGAAGCTGTTTCCTTCAGATTTAGGTTATGTGGGATGATGTGGGA
TTGAAGAGGAAAGAAAGGTGGGATTATCCCCCTAGGAAGACTTTCAGGCCTGACTTCATA
GGAATTCATCCATCTTATCATGTGGAGTTTATCTCACCCTGCTGTTGCAGGATGCTATTT
GCATGTGTCCCCAGGTGATGTTTTTTCTTTGGGGAGTAGGGGTTTGGCTTCCTCATTCAT

CCCTCTTGCTAAAAGAGGAGATAGTTGATGTTGCATCTAAAGATGCTATAAGACAATGAAAGTTTGATGTTGTAC
ATACCTACAAGTACCATTTTTGTGCATGATTACACTCCACTGACATCTTCCAAGTACTAC
ATGTGATTGAATAAGAAACAAGAAAGTGACCACACCAAAGCCTCCCTGGCTGGTGTACAG
GGATCAGGTCCACAGTGGTGCAGATTCAACCACCACCCAGGGAGTGCTTGCAGACTCTGC
ATAGATGTTGCTGCATGCGTCCCATGTGCCTGTCAGAATGGCAGTGTTTAATTCTCTTGA
AAGAAAGTTATTTGCTCACTATCCCCAGCCTCAAGGAGCCAAGGAAGAGTCATTCACATG
GAAGGTCCGGGACTGGTCAGCCACTCTGACTTTTCTACCACATTAAATTCTCCATTACAT
CTCACTATTGGTAATGGCTTAAGTGTAAAGAGCCATGATGTGTATATTAAGCTATGTGCC
ACATATTTATTTTTAGACTCTCCACAGCATTCATGTCAATATGGGATTAATGCCTAAACT
TTGTAAATATTGTACAGTTTGTAAATCAATGAATAAAGGTTTTGAGTGTAAAAAAAAAAA
AAAAAA

FIGURE 346

MEPGPALAWLLLLSLLADCLKAAQSRDFTVKDIIYLHPSTTPYPGGFKCFTCEKAADNYE
CNRWAPDIYCPRETRYCYTQHTMEVTGNSISVTKRCVPLEECLSTGCRDSEHEGHKVCTS
CCEGNICNLPLPRNETDATFATTSPINQTNGHPRCMSVIVSCLWLWLGLML

Important features of the protein:

Signal peptide:
1-22

Transmembrane domain:
None

N-glycosylation site:
134-138, 147-151

N-myristoylation site:
45-51, 87-93, 106-112, 124-130

Ly-6 / u-PAR domain protein:
115-128

FIGURE 347

GATCAAGCGCCTTCCTTTCCCTTCCTCTCCCTACTTGGCCTTTGCCCTAAGCCAAGACCT
GGCCATCAGCCTGGCTGCAGGGGCCTGCAGAGCCAGCTGCACTTTTTCAGGTATGGGGGA
GGGCCAGGCACCATGAAGCCAGTGTGGGTCGCCACCCTTCTGTGGATGCTACTGCTGGTG
CCCAGGCTGGGGGCCGCCCGGAAGGGGTCCCCAGAAGAGGCCTCCTTCTACTATGGAACC
TTCCCTCTTGGCTTCTCCTGGGGCGTGGGCAGTTCTGCCTACCAGACGGAGGGCGCCTGG
GACCAGGACGGGAAAGGGCCTAGCATCTGGGACGTCTTCACACACAGTGGGAAGGGGAAA
GTGCTTGGGAATGAGACGGCAGATGTAGCCTGTGACGGCTACTACAAGGTCCAGGAGGAC
ATCATTCTGCTGAGGGAACTGCACGTCAACCACTACCGATTCTCCCTGTCTTGGCCCCGG
CTCCTGCCCACAGGCATCCGAGCCGAGCAGGTGAACAAGAAGGGAATCGAATTCTACAGT
GATCTTATCGATGCCCTTCTGAGCAGCAACATCACTCCCATCGTGACCTTGCACCACTGG
GATCTGCCACAGCTGCTCCAGGTCAAATACGGTGGGTGGCAGAATGTGAGCATGGCCAAC
TACTTCAGAGACTACGCCAACCTGTGCTTTGAGGCCTTTGGGGACCGTGTGAAGCACTGG
ATCACGTTCAGTGATCCTCGGGCAATGGCAGAAAAAGGCTATGAGACGGGCCACCATGCG
CCGGGCCTGAAGCTCCGCGGCACCGGCCTGTACAAGGCAGCACACCACATCATTAAGGCC
CACGCCAAAACCTGGCATTCTTATAACACCACGTGGCGCAGCAAGCAGCAAGGTCTGGTG
GGAATTTCACTGAACTGTGACTGGGGGGAACCTGTGGACATTAGTAACCCCAAGGACCTA
GAGGCTGCCGAGAGATACCTACAGTTCTGTCTGGGCTGGTTTGCCAACCCCATTTATGCC
GGTGACTACCCCCAAGTCATGAAGGACTACATTGGAAGAAAGAGTGCAGAGCAAGGCCTG
GAGATGTCGAGGTTACCGGTGTTCTCACTCCAGGAGAAGAGCTACATTAAAGGCACATCC
GATTTCTTGGGATTAGGTCATTTTACTACTCGGTACATCACGGAAAGGAACTACCCCTCC
CGCCAGGGGCCCAGCTACCAGAACGATCGTGACTTGATAGAGCTGGTTGACCCAAACTGG
CCAGATCTGGGGTCTAAATGGCTATATTCTGTGCCATGGGGATTTAGGAGGCTCCTTAAC
TTTGCTCAGACTCAATACGGTGATCCTCCCATATATGTGATGGAAAATGGAGCATCTCAA
AAATTCCACTGTACTCAATTATGTGATGAGTGGAGAATTCAATACCTTAAAGGATACATA
AATGAAATGCTAAAAGCTATAAAAGATGGTGCTAATATAAAGGGGTATACTTCCTGGTCT
CTGTTGGATAAGTTTGAATGGGAGAAAGGATACTCAGATAGATATGGATTCTACTATGTT
GAATTTAACGACAGAAATAAGCCTCGCTATCCAAAGGCTTCAGTTCAATATTACAAGAAG
ATTATCATTGCCAATGGGTTTCCCAATCCAAGAGAGGTGGAAAGTTGGTACCTCAAAGCT
TTGGAAACTTGCTCTATCAACAATCAGATGCTTGCTGCAGAGCCTTTGCTAAGTCACATG
CAAATGGTTACGGAGATCGTGGTACCCACTGTCTGCTCCCTCTGTGTCCTCATCACTGCT
GTTCTACTAATGCTCCTCCTGAGGAGGCAGAGCTGAGACAGGATTATCAATTTTGGAGCT
TCATAAGAGAATCTTCAGGATCTTCCTCCCTTTTCTGCTTTGAGGGTTTCCATACATTGC
TGTTTTCAGGTTCTACAATAATTACCTTTTTTTCTCTTTCTCTTTTTGGCTTGTGCTGGG
ATTTAAGAATTAGAAAATAAAAATAAGCAGAAATTA

FIGURE 348

MKPVWVATLLWMLLLVPRLGAARKGSPEEASFYYGTFPLGFSWGVGSSAYQTEGAWDQDG
KGPSIWDVFTHSGKGKVLGNETADVACDGYYKVQEDIILLRELHVNHYRFSLSWPRLLPT
GIRAEQVNKKGIEFYSDLIDALLSSNITPIVTLHHWDLPQLLQVKYGGWQNVSMANYFRD
YANLCFEAFGDRVKHWITFSDPRAMAEKGYETGHHAPGLKLRGTGLYKAAHHIIKAHAKT
WHSYNTTWRSKQQGLVGISLNCDWGEPVDISNPKDLEAAERYLQFCLGWFANPIYAGDYP
QVMKDYIGRKSAEQGLEMSRLPVFSLQEKSYIKGTSDFLGLGHFTTRYITERNYPSRQGP
SYQNDRDLIELVDPNWPDLGSKWLYSVPWGFRRLLNFAQTQYGDPPIYVMENGASQKFHC
TQLCDEWRIQYLKGYINEMLKAIKDGANIKGYTSWSLLDKFEWEKGYSDRYGFYYVEFND
RNKPRYPKASVQYYKKIIIANGFPNPREVESWYLKALETCSINNQMLAAEPLLSHMQMVT
EIVVPTVCSLCVLITAVLLMLLLRRQS

Important features:
Signal peptide:
amino acids 1-21

Transmembrane domain:
amino acids 541-558

N-glycosylation sites:
amino acids 80-84,171-175,245-249

Glycosaminoglycan attachment site:
amino acids 72-76

cAMP- and cGMP-dependent protein kinase phosphorylation sites:
amino acids 23-27,564-568

Tyrosine kinase phosphorylation sites:
amino acids 203-211,347-355,460-468,507-514

N-myristoylation sites:
amino acids 44-50,79-85,167-173,225-231,257-263,315-321

Amidation site:
amino acids 307-311

Glycosyl hydrolases family 1 active site:
amino acids 407-416

Glycosyl hydrolases family 1 N-terminal signature:
amino acids 41-56

Motif name Glycosyl hydrolases family:
amino acids 37- 67

FIGURE 349

CGCAAAGCCGCCCTCGGGGCGCTCATGGCGGGACGCCTCCTGGGAAAGGCTTTAGCCGCG
GTGTCTCTCTCTCTGGCCTTGGCCTCTGTGACTATCAGGTCCTCGCGCTGCCGCGGCATC
CAGGCGTTCAGAAACTCGTTTTCATCTTCTTGGTTTCATCTTAATACCAACGTCATGTCT
GGTTCTAATGGTTCCAAAGAAAATTCTCACAATAAGGCTCGGACGTCTCCTTACCCAGGT
TCAAAAGTTGAACGAAGCCAGGTTCCTAATGAGAAAGTGGGCTGGCTTGTTGAGTGGCAA
GACTATAAGCCTGTGGAATACACTGCAGTCTCTGTCTTGGCTGGACCCAGGTGGGCAGAT
CCTCAGATCAGTGAAAGTAATTTTTCTCCCAAGTTTAACGAAAAGGATGGGCATGTTGAG
AGAAAGAGCAAGAATGGCCTGTATGAGATTGAAAATGGAAGACCGAGAAATCCTGCAGGA
CGGACTGGACTGGTGGGCCGGGGGCTTTTGGGGCGATGGGGCCCAAATCACGCTGCAGAT
CCCATTATAACCAGATGGAAAAGGGATAGCAGTGGAAATAAAATCATGCATCCTGTTTCT
GGGAAGCATATCTTACAATTTGTTGCAATAAAAAGGAAAGACTGTGGAGAATGGGCAATC
CCAGGGGGGATGGTGGATCCAGGAGAGAAGATTAGTGCCACACTGAAAAGAGAATTTGGT
GAGGAAGCTCTCAACTCCTTACAGAAAACCAGTGCTGAGAAGAGAGAAATAGAGGAAAAG
TTGCACAAACTCTTCAGCCAAGACCACCTAGTGATATATAAGGGATATGTTGATGATCCT
CGAAACACTGATAATGCATGGATGGAGACAGAAGCTGTGAACTACCATGACGAAACAGGT
GAGATAATGGATAATCTTATGCTAGAAGCTGGAGATGATGCTGGAAAAGTGAAATGGGTG
GACATCAATGATAAACTGAAGCTTTATGCCAGTCACTCTCAATTCATCAAACTTGTGGCT
GAGAAACGAGATGCACACTGGAGCGAGGACTCTGAAGCTGACTGCCATGCGTTGTAGCTG
ATGGTCTCCGTGTAAGCCAAAGGCCCACAGAGGAGCATATACTGAAAAGAAGGCAGTATC
ACAGAATTTATACTATAAAAAGGGCAGGGTAGGCCACTTGGCCTATTTACTTTCAAAACA
ATTTGCATTTAGAGTGTTTCGCATCAGAATAACATGAGTAAGATGAACTGGAACACAAAA
TTTTCAGCTCTTTGGTCAAAAGGAATATAAGTAATCATATTTTGTATGTATTCGATTTAA
GCATGGCTTAAATTAAATTTAAACAACTAATGCTCTTTGAAGAATCATAATCAGAATAAA
GATAAATTCTTGATCAGCTATA

FIGURE 350

MAGRLLGKALAAVSLSLALASVTIRSSRCRGIQAFRNSFSSSWFHLNTNVMSGSNGSKEN
SHNKARTSPYPGSKVERSQVPNEKVGWLVEWQDYKPVEYTAVSVLAGPRWADPQISESNF
SPKFNEKDGHVERKSKNGLYEIENGRPRNPAGRTGLVGRGLLGRWGPNHAADPIITRWKR
DSSGNKIMHPVSGKHILQFVAIKRKDCGEWAIPGGMVDPGEKISATLKREFGEEALNSLQ
KTSAEKREIEEKLHKLFSQDHLVIYKGYVDDPRNTDNAWMETEAVNYHDETGEIMDNLML
EAGDDAGKVKWVDINDKLKLYASHSQFIKLVAEKRDAHWSEDSEADCHAL

Important features of the protein:

Signal peptide:
1-20

Transmembrane domain:
None

N-glycosylation site:
55-59

cAMP- and cGMP-dependent protein kinase phosphorylation site:
179-183

N-myristoylation site:
53-59, 56-62

mutT domain signature:
215-235

FIGURE 351

CCTCTGTCTGTGCTCCCATCCCAGGGAGTATAGGTGGAGCCTCCAGAGCCCATGGACAGG
GCATGCTGGGGCTGGGCCAGCCCCAGCGGTGTCTCTAAGGCACCCCTGGGATCCCCACTG
AGCTGGCCTACTTCAGACAGCCAGGGCCCACCCCTCTGGCCCCCTTAGTGTCCAGCTCGT
GGCCCCTTGGCATTTCCACAAGACGCCAAG**ATG**GAGATTCCCATGGGGACCCAGGGCTGC
TTCTCAAAGAGCCTCCTGCTCTCAGCCTCAATCCTGGTCCTCTGGATGCTCCAAGGCTCC
CAGGCAGCTCTCTACATCCAGAAGATTCCAGAGCAGCCTCAAAAGAACCAGGACCTTCTC
CTGTCAGTCCAGGGTGTCCCAGACACCTTCCAGGACTTCAACTGGTACCTGGGGGAGGAG
ACGTACGGAGGCACGAGGCTATTTACCTACATCCCTGGGATACAACGGCCTCAGAGGGAT
GGCAGTGCCATGGGACAGCGAGACATCGTGGGCTTCCCCAATGGTTCCATGCTGCTGCGC
CGCGCCCAGCCTACAGACAGTGGCACCTACCAAGTAGCCATTACCATCAACTCTGAATGG
ACTATGAAGGCCAAGACTGAGGTCCAGGTAGCTGAAAAGAATAAGGAGCTGCCCAGTACA
CACCTGCCCACCAACGCTGGGATCCTGGCGGCCACCATCATTGGATCTCTTGCTGCCGGG
GCCCTTCTCATCAGCTGCATTGCCTATCTCCTGGTGACAAGGAACTGGAGGGGCCAGAGC
CACAGACTGCCTGCTCCGAGGGGCCAGGGATCTCTGTCCATCTTGTGCTCGGCTGTATCC
CCAGTGCCTTCAGTGACGCCCAGCACATGGATGGCGACCACAGAGAAGCCAGAATTGGGC
CCTGCTCATGATGCTGGTGACAACAACATCTATGAAGTGATGCCCTCTCCAGTCCTCCTG
GTGTCCCCCATCAGTGACACAAGGTCCATAAACCCAGCCCGGCCCCTGCCCACACCCCCA
CACCTGCAGGCGGAGCCAGAGAACCACCAGTACCAGCAGGACCTGCTAAACCCCGACCCT
GCCCCCTACTGCCAGCTGGTGCCAACTTCC**TGA**TGGGTCCTGGGCCAGGCCAGCCAGGGA
GAAGACAAGGCCCCAGCCCTCCTCTGGGAGCCTCACACCTGAGACCAGCAGGACAAGGCC
ATTGGGGGCTGTGGGGCCGATGAGGTGGACTCAGCCAAAGACTCAGCAGCACATGGGGCA
GGTGTCCTGGCAGGGGGACAGGAGACTGTAACAGGCCCAGGTCCTTGTGCAGCCCCTGAA
TGCACGCCCGCCTTCGGTCTGTTCCTTCAAGCAAGCTGGCCTGGGCCATGTGCCTGTGAA
AGGCAGGCTCTGGCCCCTTTCCATGCCAAAGTCCCCCAAGATCTGGATATCTGGGGACAA
GATGGTGGCCTCAGGCCTGCCTCCCAGGCAGTTGGCTGGGCTCCCAACTGTCTGTCCTCA
ATGCCCTACCCCAACTCCACTAGTGACCCTCAGAGTCTTCTCCCCTTAGGACAAGGCAGA
CACCCCACCATGCGGGCCTCAGGTGGCAGAGAGGCCCAGCCTCACAGGCCTGTGGCCCCA
CACACCAGTCCCAGCAAGGTGACCACGGCTGCTGGACCCCTTCCCTGTTCAGGCAGGCCC
AGCCCCTCTCAGAACCTGCTGCCAGCTGCTGGTCTTGGCCCCCACCCTGAATCTTACTGA
GTCCCTCTGGGCAGCAGCTCCCTTCTCCACCCCACCCCAGCACCCGTCCCAAATGTGGCC
TCAGCTTGTCCTCCCCTTCCCCAAACTATGCATTCATTCAGCAATAAATGAGCCTTTGCT
GCA

FIGURE 352

MEIPMGTQGCFSKSLLLSASILVLWMLQGSQAALYIQKIPEQPQKNQDLLLSVQGVPDTF
QDFNWYLGEETYGGTRLFTYIPGIQRPQRDGSAMGQRDIVGFPNGSMLLRRAQPTDSGTY
QVAITINSEWTMKAKTEVQVAEKNKELPSTHLPTNAGILAATIIGSLAAGALLISCIAYL
LVTRNWRGQSHRLPAPRGQGSLSILCSAVSPVPSVTPSTWMATTEKPELGPAHDAGDNNI
YEVMPSPVLLVSPISDTRSINPARPLPTPPHLQAEPENHQYQQDLLNPDPAPYCQLVPTS

Important features of the protein:
Signal peptide:
Amino acids 1-32

Transmembrane domain:
Amino acids 159-178

N-glycosylation site:
Amino acids 104-108

N-myristoylation sites:
Amino acids 6-12;29-35;55-61;91-97;157-163;165-171

FIGURE 353

CTTCAGAACAGGTTCTCCTTCCCCAGTCACCAGTTGCTCGAGTTAGAATTGTCTGCAATG
GCCGCCCTGCAGAAATCTGTGAGCTCTTTCCTTATGGGGACCCTGGCCACCAGCTGCCTC
CTTCTCTTGGCCCTCTTGGTACAGGGAGGAGCAGCTGCGCCCATCAGCTCCCACTGCAGG
CTTGACAAGTCCAACTTCCAGCAGCCCTATATCACCAACCGCACCTTCATGCTGGCTAAG
GAGGCTAGCTTGGCTGATAACAACACAGACGTTCGTCTCATTGGGGAGAAACTGTTCCAC
GGAGTCAGTATGAGTGAGCGCTGCTATCTGATGAAGCAGGTGCTGAACTTCACCCTTGAA
GAAGTGCTGTTCCCTCAATCTGATAGGTTCCAGCCTTATATGCAGGAGGTGGTGCCCTTC
CTGGCCAGGCTCAGCAACAGGCTAAGCACATGTCATATTGAAGGTGATGACCTGCATATC
CAGAGGAATGTGCAAAAGCTGAAGGACACAGTGAAAAAGCTTGGAGAGAGTGGAGAGATC
AAAGCAATTGGAGAACTGGATTTGCTGTTTATGTCTCTGAGAAATGCCTGCATTTGACCA
GAGCAAAGCTGAAAAATGAATAACTAACCCCCTTTCCCTGCTAGAAATAACAATTAGATG
CCCCAAAGCGATTTTTTTAACCAAAAGGAAGATGGGAAGCCAAACTCCATCATGATGGG
TGGATTCCAAATGAACCCCTGCGTTAGTTACAAAGGAAACCAATGCCACTTTTGTTTATA
AGACCAGAAGGTAGACTTTCTAAGCATAGATATTTATTGATAACATTTCATTGTAACTGG
TGTTCTATACACAGAAAACAATTTATTTTTTAAATAATTGTCTTTTTCCATAAAAAAGAT
TACTTTCCATTCCTTTAGGGGAAAAAACCCCTAAATAGCTTCATGTTTCCATAATCAGTA
CTTTATATTTATAAATGTATTTATTATTATTATAAGACTGCATTTTATTTATATCATTTT
ATTAATATGGATTTATTTATAGAAACATCATTCGATATTGCTACTTGAGTGTAAGGCTAA
TATTGATATTTATGACAATAATTATAGAGCTATAACATGTTTATTTGACCTCAATAAACA
CTTGGATATCCC

FIGURE 354

MAALQKSVSSFLMGTLATSCLLLLALLVQGGAAAPISSHCRLDKSNFQQPYITNRTFMLA
KEASLADNNTDVRLIGEKLFHGVSMSERCYLMKQVLNFTLEEVLFPQSDRFQPYMQEVVP
FLARLSNRLSTCHIEGDDLHIQRNVQKLKDTVKKLGESGEIKAIGELDLLFMSLRNACI

Important features of the protein:
Signal peptide:
amino acids 1-33

N-glycosylation sites:
amino acids 54-58, 68-72, 97-101

N-myristoylation sites:
amino acids 14-20, 82-88

Prokaryotic membrane lipoprotein lipid attachment site:
amino acids 10-21

FIGURE 355

TGGCCTACTGGAAAAAAAAAAAAAAAAAAAAAAAAGTCACCCGGGCCCGCGGTGGCCACAA
C**ATG**GCTGCGGCGCCGGGGCTGCTCTTCTGGCTGTTCGTGCTGGGGGCGCTCTGGTGGGT
CCCGGGCCAGTCGGATCTCAGCCACGGACGGCGTTTCTCGGACCTCAAAGTGTGCGGGGA
CGAAGAGTGCAGCATGTTAATGTACCGTGGGAAAGCTCTTGAAGACTTCACGGGCCCTGA
TTGTCGTTTTGTGAATTTTAAAAAAGGTGACGATGTATATGTCTACTACAAACTGGCAGG
GGGATCCCTTGAACTTTGGGCTGGAAGTGTTGAACACAGTTTTGGATATTTTCCAAAAGA
TTTGATCAAGGTACTTCATAAATACACGGAAGAAGAGCTACATATTCCAGCAGATGAGAC
AGACTTTGTCTGCTTTGAAGGAGGAAGAGATGATTTTAATAGTTATAATGTAGAAGAGCT
TTTAGGATCTTTGGAACTGGAGGACTCTGTACCTGAAGAGTCGAAGAAAGCTGAAGAAGT
TTCTCAGCACAGAGAGAAATCTCCTGAGGAGTCTCGGGGGCGTGAACTTGACCCTGTGCC
TGAGCCCGAGGCATTCAGAGCTGATTCAGAGGATGGAGAAGGTGCTTTCTCAGAGAGCAC
CGAGGGGCTGCAGGGACAGCCCTCAGCTCAGGAGAGCCACCCTCACACCAGCGGTCCTGC
GGCTAACGCTCAGGGAGTGCAGTCTTCGTTGGACACTTTTGAAGAAATTCTGCACGATAA
ATTGAAAGTGCCGGGAAGCGAAAGCAGAACTGGCAATAGTTCTCCTGCCTCGGTGGAGCG
GGAGAAGACAGATGCTTACAAAGTCCTGAAAACAGAAATGAGTCAGAGAGGAAGTGGACA
GTGCGTTATTCATTACAGCAAAGGATTTCGTTGGCATCAAAATCTAAGTTTGTTTTACAA
AGATTGTTTT**TAG**TACTAAGCTGCCTTGGCAGTTTGCATTTTTGAGCCAAACAAAAATAT
ATTATTTTCCCTTCTAAGTAAAAAAAAAAAAAAAAAAAAA

FIGURE 356

MAAAPGLLFWLFVLGALWWVPGQSDLSHGRRFSDLKVCGDEECSMLMYRGKALEDFTGPD
CRFVNFKKGDDVYVYYKLAGGSLELWAGSVEHSFGYFPKDLIKVLHKYTEEELHIPADET
DFVCFEGGRDDFNSYNVEELLGSLELEDSVPEESKKAEEVSQHREKSPEESRGRELDPVP
EPEAFRADSEDGEGAFSESTEGLQGQPSAQESHPHTSGPAANAQGVQSSLDTFEEILHDK
LKVPGSESRTGNSSPASVEREKTDAYKVLKTEMSQRGSGQCVIHYSKGFRWHQNLSLFYK
DCF

Important features of the protein:
Signal peptide:
amino acids 1-22

N-glycosylation site:
amino acids 294-298

cAMP- and cGMP-dependent protein kinase phosphorylation site:
amino acids 30-34

Tyrosine kinase phosphorylation site:
amino acids 67-76

N-myristoylation sites:
amino acids 205-211, 225-231, 277-283

Amidation site:
amino acids 28-32

FIGURE 357

ACGCGCCCGGCAGCTGTCCACCGATCCCGGCCACCGCCCCCGGCCACCCCCACCCCGCGA
GCCC**ATG**GAGGCTCCGGGACCCCGCGCCTTGCGGACTGCGCTCTGTGGCGGCTGTTGCTG
CCTCCTCCTATGTGCCCAGCTGGCTGTGGCTGGTAAAGGAGCTCGAGGCTTTGGGAGGGG
AGCCCTGATCCGCCTGAATATCTGGCCGGCGGTCCAAGGGGCCTGCAAACAGCTGGAGGT
CTGTGAGCACTGCGTGGAGGGAGACAGAGCGCGCAATCTCTCCAGCTGCATGTGGGAGCA
GTGCCGGCCAGAGGAGCCAGGACACTGTGTGGCCCAATCTGAGGTGGTCAAGGAAGGTTG
CTCCATCTACAACCGCTCAGAGGCATGTCCAGCTGCTCACCACCACCCCACCTATGAACC
GAAGACAGTCACAACAGGGAGCCCCCCAGTCCCTGAGGCCCACAGCCCTGGATTTGACGG
GGCCAGCTTTATCGGAGGTGTCGTGCTGGTGTTGAGCCTACAGGCGGTGGCTTTCTTTGT
GCTGCACTTCCTCAAGGCCAAGGACAGCACCTACCAGACGCTG**TGA**GTACCTGGCCAGCA
GCAAGTACCTGAGTCCCAGCTCACCTCCTGGTTCCTGCCCCACCGTTCCCCTTCAGTACC
CAGGGTGCTGTCTTCTCCATGGGCAAGCCCTCAGGACGGTGACAGCGTGCTCCATGTGAG
CCACACCCCTTTTGTCTCCTCCAGTTGGGGTGTTTCCTTTGTCAGATGTTGGCTGGGACC
AGGACTCAGCCTGGGCCAGTCTAGGAGCCCAGCTGAGCCCTCCTGTGTCTTTTCCCTTCA
TGCTGCCAGCAGGGAAGAGAACCAGTAGGTGCCAGCCCAGGCAAGCCTGTGGCCCGCGTT
TCTGTGGCTGTGGGCAGGAGCTGGGCCTTGTGTCTAGTTGGGTTTTGCTCTGAGAAGGGG
AGCTGTGCCTGAGGCCCTCTGTGTGCCGTGTGTGCTGTGGGGCGGGTCGCCACAGCCTGT
GTTAAAGTGTTTGCTCTTCCTCTGCTGCCTCCTCTCGAGGCAGGGGGTCCTTGGCTGGCT
GAGGCAGTGTCACCTTCCTGAGTGTCCTCTTTGGCCTCTGCAGAATCTGACCCCTTTGGG
CCTGGACTCCATCCTGAGGGGAAAGGAGGATGCAGAGGGTGGCCTCTGGGCACCCTTGTG
GGTAAGCGGGGGGCGGGGGCGGGAAAAACTCTGGCCGCCAGTTTTTGGCTCCTGCGGGCA
CCAAGCAGGCTCAGTGTCTGATGCCTGACATCTCCTCCTGTCCTGGGCCTGGAACCTGCA
GCTGAGAAAATCCCTCAACCACCTCGTCTCCTCCATCGCCCCTGCTGGGCCCCCCAGCCT
GACAGTGGGTTGTATGCCTGCCTCTTTCCACCAACTGGCCTGGGCACTGCCCCCAAATAA
AGGAACTCTGCACTGCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAAAAAAAAAAAACCA

FIGURE 358

MEAPGPRALRTALCGGCCCLLLCAQLAVAGKGARGFGRGALIRLNIWPAVQGACKQLEVC
EHCVEGDRARNLSSCMWEQCRPEEPGHCVAQSEVVKEGCSIYNRSEACPAAHHHPTYEPK
TVTTGSPPVPEAHSPGFDGASFIGGVVLVLSLQAVAFFVLHFLKAKDSTYQTL

Important features of the protein:

Signal peptide:
1-29

Transmembrane domain:
141-160

N-glycosylation site:
71-75, 103-107

Tyrosine kinase phosphorylation site:
164-171

N-myristoylation site:
15-21

FIGURE 359

TTCCAGTCAGAGTTAAGTTAAAACAGAAAAAAGGAAG<u>ATG</u>GCAAGAATATTGTTACTTTT
CCTCCCGGGTCTTGTGGCTGTATGTGCTGTGCATGGAATATTTATGGACCGTCTAGCTTC
CAAGAAGCTCTGTGCAGATGATGAGTGTGTCTATACTATTTCTCTGGCTAGTGCTCAAGA
AGATTATAATGCCCCGGACTGTAGATTCATTAACGTTAAAAAAGGGCAGCAGATCTATGT
GTACTCAAAGCTGGTAAAAGAAAATGGAGCTGGAGAATTTTGGGCTGGCAGTGTTTATGG
TGATGGCCAGGACGAGATGGGAGTCGTGGGTTATTTCCCCAGGAACTTGGTCAAGGAACA
GCGTGTGTACCAGGAAGCTACCAAGGAAGTTCCCACCACGGATATTGACTTCTTCTGCGA
G<u>TAA</u>TAAATTAGTTAAAACTGCAAATAGAAAGAAAACACCAAAAATAAAGAAAAGAGCAA
AAGTGGCCAAAAAATGCATGTCTGTAATTTTGGACTGACGT

FIGURE 360

MARILLLFLPGLVAVCAVHGIFMDRLASKKLCADDECVYTISLASAQEDYNAPDCRFINV
KKGQQIYVYSKLVKENGAGEFWAGSVYGDGQDEMGVVGYFPRNLVKEQRVYQEATKEVPT
TDIDFFCE

Important features of the protein:

Signal peptide:
1-14

Transmembrane domain:
None

N-myristoylation site:
84-90

FIGURE 361

GGCACGAGCCACCACTTACAACCACACAGCCTATCCAGAAACATGAAGATAAGAAATGCT
TGTGCTGTCCTTATTGAAGTACTCCTGTTTATACTTGAAGGAGTTACAGGAGCTCGAAAA
ATTTCAACTTTCTCAGGCCCTGGCTCATGGCCGTGCAATCCCAAGTGTGATGGCAGAACT
TACAACCCCTCAGAGGAGTGTTGTGTTCATGACACCATCCTGCCCTTTAAGCGGATTAAC
CTCTGTGGCCCTAGCTGCACCTACAGGCCCTGCTTTGAGCTCTGCTGTCCTGAGTCCTAT
AGCCCCAAGAAGAAATTTATTGTCAAGCTTAAAGTTCATGGAGAGAGATCCCATTGCAGT
TCATCCCCTATCTCCAGGAACTGTAAAAGCAACAAGATTTTTCATGGAGAAGATATTGAA
GACAACCAACTTTCTCTTAGGAAAAAAAGTGGTGACCAGCCTTGAGAGTCTGCTTTCTTC
CTGCAAGCACCAGTTCCTGAATGTTCTTACTTGAAGAATGGATACCTGAAGCATTGGGGT
GCAGTGATATATGTGTCTCATTACAATGCTCCTTTGGATATTGTTTTCCTAAGCATGTGT
TGGAATGTTCCCCCATAACTTTCTAAAATTATCCTATTTCAATGCAACTAAAGATAAATG
TATTCCAGCCAGAGTCCACAGAGAAGGCAAGTTATGCAAGGCAGGCATGGGGCCCTCACA
AAATTTCAAGCTGTGCGACTTATGTAGTAATTTTCTACAAACAATCCCTCCTGGATATCC
AGGAGGCTCCAGACCTGAATAAAAACCACATGTCTGTCTAGAAAAAGGGAATGAATCAAG
ATCCACAGGACCTTTTCAAGATTTTAGAAGCAGCAAACTATGGCTGAGAGAAAAGACTCT
CTGACCAGGCAAATTGTTCTGCAGTATTCTCCGGGCGTGTAGCTCCCCTGAGTAGTCGCC
AGGCTGGTCTTGGCTTTGTAATAATACAGCTGCCTTTGAGTCCTCCCTACCCTGTTAGTA
ACCCCTTGCCTGCACTGTTGTCCTTACAACCGAAATAAACTGATTAGTTG

FIGURE 362

MKIRNACAVLIEVLLFILEGVTGARKISTFSGPGSWPCNPKCDGRTYNPSEECCVHDTIL
PFKRINLCGPSCTYRPCFELCCPESYSPKKKFIVKLKVHGERSHCSSSPISRNCKSNKIF
HGEDIEDNQLSLRKKSGDQP

Important features of the protein:

Signal peptide:
1-23

Transmembrane domain:
None

Glycosaminoglycan attachment site:
31-35

N-myristoylation site:
20-26, 34-40

FIGURE 363

ACACTGGCCAAACAAAAACGAAAGCACTCCGTGCTGGAAGTAGGAGGAGAGTCAGGACTC
CCAGGACAGAGAGTGCACAAACTACCCAGCACAGCCCCCTCCGCCCCCTCTGGAGGCTGA
AGAGGGATTCCAGCCCCTGCCACCCACAGACACGGGCTGACTGGGGTGTCTGCCCCCCTT
GGGGGGGGGCAGCACAGGGCCTCAGGCCTGGGTGCCACCTGGCACCTAGAAG**ATG**CCTGT
GCCCTGGTTCTTGCTGTCCTTGGCACTGGGCCGAAGCCCAGTGGTCCTTTCTCTGGAGAG
GCTTGTGGGGCCTCAGGACGCTACCCACTGCTCTCCGGGCCTCTCCTGCCGCCTCTGGGA
CAGTGACATACTCTGCCTGCCTGGGGACATCGTGCCTGCTCCGGGCCCCGTGCTGGCGCC
TACGCACCTGCAGACAGAGCTGGTGCTGAGGTGCCAGAAGGAGACCGACTGTGACCTCTG
TCTGCGTGTGGCTGTCCACTTGGCCGTGCATGGGCACTGGGAAGAGCCTGAAGATGAGGA
AAAGTTTGGAGGAGCAGCTGACTCAGGGGTGGAGGAGCCTAGGAATGCCTCTCTCCAGGC
CCAAGTCGTGCTCTCCTTCCAGGCCTACCCTACTGCCCGCTGCGTCCTGCTGGAGGTGCA
AGTGCCTGCTGCCCTTGTGCAGTTTGGTCAGTCTGTGGGCTCTGTGGTATATGACTGCTT
CGAGGCTGCCCTAGGGAGTGAGGTACGAATCTGGTCCTATACTCAGCCCAGGTACGAGAA
GGAACTCAACCACACACAGCAGCTGCCTGCCCTGCCCTGGCTCAACGTGTCAGCAGATGG
TGACAACGTGCATCTGGTTCTGAATGTCTCTGAGGAGCAGCACTTCGGCCTCTCCCTGTA
CTGGAATCAGGTCCAGGGCCCCCCAAAACCCCGGTGGCACAAAAACCTGACTGGACCGCA
GATCATTACCTTGAACCACACAGACCTGGTTCCCTGCCTCTGTATTCAGGTGTGGCCTCT
GGAACCTGACTCCGTTAGGACGAACATCTGCCCCTTCAGGGAGGACCCCCGCGCACACCA
GAACCTCTGGCAAGCCGCCCGACTGCGACTGCTGACCCTGCAGAGCTGGCTGCTGGACGC
ACCGTGCTCGCTGCCCGCAGAAGCGGCACTGTGCTGGCGGGCTCCGGGTGGGGACCCCTG
CCAGCCACTGGTCCCACCGCTTTCCTGGGAGAACGTCACTGTGGACAAGGTTCTCGAGTT
CCCATTGCTGAAAGGCCACCCTAACCTCTGTGTTCAGGTGAACAGCTCGGAGAAGCTGCA
GCTGCAGGAGTGCTTGTGGGCTGACTCCCTGGGGCCTCTCAAAGACGATGTGCTACTGTT
GGAGACACGAGGCCCCCAGGACAACAGATCCCTCTGTGCCTTGGAACCCAGTGGCTGTAC
TTCACTACCCAGCAAAGCCTCCACGAGGGCAGCTCGCCTTGGAGAGTACTTACTACAAGA
CCTGCAGTCAGGCCAGTGTCTGCAGCTATGGGACGATGACTTGGGAGCGCTATGGGCCTG
CCCCATGGACAAATACATCCACAAGCGCTGGGCCCTCGTGTGGCTGGCCTGCCTACTCTT
TGCCGCTGCGCTTTCCCTCATCCTCCTTCTCAAAAAGGATCACGCGAAAGGGTGGCTGAG
GCTCTTGAAACAGGACGTCCGCTCGGGGGCGGCCGCCAGGGGCCGCGCGGCTCTGCTCCT
CTACTCAGCCGATGACTCGGGTTTCGAGCGCCTGGTGGGCGCCCTGGCGTCGGCCCTGTG
CCAGCTGCCGCTGCGCGTGGCCGTAGACCTGTGGAGCCGTCGTGAACTGAGCGCGCAGGG
GCCCGTGGCTTGGTTTCACGCGCAGCGGCGCCAGACCCTGCAGGAGGGCGGCGTGGTGGT
CTTGCTCTTCTCTCCCGGTGCGGTGGCGCTGTGCAGCGAGTGGCTACAGGATGGGGTGTC
CGGGCCCGGGGCGCACGGCCCGCACGACGCCTTCCGCGCCTCGCTCAGCTGCGTGCTGCC
CGACTTCTTGCAGGGCCGGGCGCCCGGCAGCTACGTGGGGGCCTGCTTCGACAGGCTGCT
CCACCCGGACGCCGTACCCGCCCTTTTCCGCACCGTGCCCGTCTTCACACTGCCCTCCCA
ACTGCCAGACTTCCTGGGGGCCCTGCAGCAGCCTCGCGCCCCGCGTTCCGGGCGGCTCCA
AGAGAGAGCGGAGCAAGTGTCCCGGGCCCTTCAGCCAGCCCTGGATAGCTACTTCCATCC
CCCGGGGACTCCCGCGCCGGGACGCGGGGTGGGACCAGGGGCGGGACCTGGGGCGGGGGA
CGGGACT**TAA**ATAAAGGCAGACGCTGTTTTTCTAAAAAAA

FIGURE 364

MPVPWFLLSLALGRSPVVLSLERLVGPQDATHCSPGLSCRLWDSDILCLPGDIVPAPGPV
LAPTHLQTELVLRCQKETDCDLCLRVAVHLAVHGHWEEPEDEEKFGGAADSGVEEPRNAS
LQAQVVLSFQAYPTARCVLLEVQVPAALVQFGQSVGSVVYDCFEAALGSEVRIWSYTQPR
YEKELNHTQQLPALPWLNVSADGDNVHLVLNVSEEQHFGLSLYWNQVQGPPKPRWHKNLT
GPQIITLNHTDLVPCLCIQVWPLEPDSVRTNICPFREDPRAHQNLWQAARLRLLTLQSWL
LDAPCSLPAEAALCWRAPGGDPCQPLVPPLSWENVTVDKVLEFPLLKGHPNLCVQVNSSE
KLQLQECLWADSLGPLKDDVLLLETRGPQDNRSLCALEPSGCTSLPSKASTRAARLGEYL
LQDLQSGQCLQLWDDDLGALWACPMDKYIHKRWALVWLACLLFAAALSLILLLKKDHAKG
WLRLLKQDVRSGAAARGRAALLLYSADDSGFERLVGALASALCQLPLRVAVDLWSRRELS
AQGPVAWFHAQRRQTLQEGGVVVLLFSPGAVALCSEWLQDGVSGPGAHGPHDAFRASLSC
VLPDFLQGRAPGSYVGACFDRLLHPDAVPALFRTVPVFTLPSQLPDFLGALQQPRAPRSG
RLQERAEQVSRALQPALDSYFHPPGTPAPGRGVGPGAGPGAGDGT

Signal sequence:
amino acids 1-20

Transmembrane domain:
amino acids 453-475

N-glycosylation sites:
amino acids 118-121, 186-189, 198-201, 211-214, 238-241, 248-251, 334-337, 357-360, 391-394

Glycosaminoglycan attachment site:
amino acids 583-586

cAMP- and cGMP-dependent protein kinase phosphorylation site:
amino acids 552-555

N-myristoylation sites:
amino acids 107-112, 152-157, 319-324, 438-443, 516-521, 612-617, 692-697, 696-701, 700-705

FIGURE 365

AATAGAAGTCCTCAGGACGGAGCAGAGGTGGCCGGCGGGCCCGGCTGACTGCGCCTCTGC
TTTCTTTCCATAACCTTTTCTTTCGGACTCGAATCACGGCTGCTGCGAAGGGTCTAGTTC
CGGACACTAGGGTGCCCGAACGCGCTGATGCCCCGAGTGCTCGCAGGGCTTCCCGCTAAC
C**ATG**CTGCCGCCGCCGCGGCCCGCAGCTGCCTTGGCGCTGCCTGTGCTCCTGCTACTGCT
GGTGGTGCTGACGCCGCCCCCGACCGGCGCAAGGCCATCCCCAGGCCCAGATTACCTGCG
GCGCGGCTGGATGCGGCTGCTAGCGGAGGGCGAGGGCTGCGCTCCCTGCCGGCCAGAAGA
GTGCGCCGCGCCGCGGGGCTGCCTGGCGGGCAGGGTGCGCGACGCGTGCGGCTGCTGCTG
GGAATGCGCCAACCTCGAGGGCCAGCTCTGCGACCTGGACCCCAGTGCTCACTTCTACGG
GCACTGCGGCGAGCAGCTTGAGTGCCGGCTGGACACAGGCGGCGACCTGAGCCGCGGAGA
GGTGCCGGAACCTCTGTGTGCCTGTCGTTCGCAGAGTCCGCTCTGCGGGTCCGACGGTCA
CACCTACTCCCAGATCTGCCGCCTGCAGGAGGCGGCCCGCGCTCGGCCCGATGCCAACCT
CACTGTGGCACACCCGGGGCCCTGCGAATCGGGGCCCCAGATCGTGTCACATCCATATGA
CACTTGGAATGTGACAGGGCAGGATGTGATCTTTGGCTGTGAAGTGTTTGCCTACCCCAT
GGCCTCCATCGAGTGGAGGAAGGATGGCTTGGACATCCAGCTGCCAGGGGATGACCCCCA
CATCTCTGTGCAGTTTAGGGGTGGACCCCAGAGGTTTGAGGTGACTGGCTGGCTGCAGAT
CCAGGCTGTGCGTCCCAGTGATGAGGGCACTTACCGCTGCCTTGGCCGCAATGCCCTGGG
TCAAGTGGAGGCCCCTGCTAGCTTGACAGTGCTCACACCTGACCAGCTGAACTCTACAGG
CATCCCCCAGCTGCGATCACTAAACCTGGTTCCTGAGGAGGAGGCTGAGAGTGAAGAGAA
TGACGATTACTAC**TAG**GTCCAGAGCTCTGGCCCATGGGGGTGGGTGAGCGGCTATAGTGT
TCATCCCTGCTCTTGAAAAGACCTGGAAAGGGGAGCAGGGTCCCTTCATCGACTGCTTTC
ATGCTGTCAGTAGGGATGATCATGGGAGGCCTATTTGACTCCAAGGTAGCAGTGTGGTAG
GATAGAGACAAAAGCTGGAGGAGGGTAGGGAGAGAAGCTGAGACCAGGACCGGTGGGGTA
CAAAGGGGCCCATGCAGGAGATGCCCTGGCCAGTAGGACCTCCAACAGGTTGTTTCCCAG
GCTGGGGTGGGGGCCTGAGCAGACACAGAGGTGCAGGCACCAGGATTCTCCACTTCTTCC
AGCCCTGCTGGGCCACAGTTCTAACTGCCCTTCCTCCCAGGCCCTGGTTCTTGCTATTTC
CTGGTCCCCAACGTTTATCTAGCTTGTTTGCCCTTTCCCCAAACTCATCTTCCAGAACTT
TTCCCTCTCTCCTAAGCCCCAGTTGCACCTACTAACTGCAGTCCCTTTTGCTGTCTGCCG
TCTTTTGTACAAGAGAGAGAACAGCGGAGCATGACTTAGTTCAGTGCAGAGAGATTT

FIGURE 366

MLPPPRPAAALALPVLLLLLVVLTPPPTGARPSPGPDYLRRGWMRLLAEGEGCAPCRPEE
CAAPRGCLAGRVRDACGCCWECANLEGQLCDLDPSAHFYGHCGEQLECRLDTGGDLSRGE
VPEPLCACRSQSPLCGSDGHTYSQICRLQEAARARPDANLTVAHPGPCESGPQIVSHPYD
TWNVTGQDVIFGCEVFAYPMASIEWRKDGLDIQLPGDDPHISVQFRGGPQRFEVTGWLQI
QAVRPSDEGTYRCLGRNALGQVEAPASLTVLTPDQLNSTGIPQLRSLNLVPEEEAESEEN
DDYY

Important features of the protein:

Signal peptide:
1-30

Transmembrane domain:
None

N-glycosylation site:
159-163, 183-187, 277-281

Tyrosine kinase phosphorylation site:
244-252

N-myristoylation site:
52-58, 66-72, 113-119, 249-255

Kazal-type serine protease inhibitor domain:
121-168

Immunoglobulin domain:
186-255

Insulin-like growth factor binding proteins:
53-90

FIGURE 367

AGACGCTACAGG**ATG**GAGCGGGGCGCAGGAGCCAAGCTGCTGCCGCTGCTGCTGCTTCTG
CGGGCGACTGGTTTCACATGTGCACAGACAGATGGCCGGAACGGCTACACGGCGGTCATC
GAAGTGACCAGCGGGGGTCCCTGGGGCGACTGGGCCTGGCCTGAGATGTGTCCCGATGGA
TTCTTCGCCAGCGGGTTCTCGCTCAAGGTGGAGCCTCCCCAAGGCATTCCTGGCGACGAC
ACTGCACTGAATGGGATCAGGCTGCACTGCGCGCGCGGGAACGTCCTAGGCAATACGCAC
GTGGTAGAGTCCCAGTCTGGAAGCTGGGGCGAATGGAGTGAGCCGCTGTGGTGTCGCGGC
GGCGCCTACCTAGTGGCTTTCTCGCTTCGCGTGGAGGCACCCACGACCCTCGGTGACAAC
ACAGCAGCGAACAACGTGCGCTTCCGCTGTTCAGACGGCGAGGAACTGCAGGGGCCTGGG
CTGAGCTGGGGAGACTTTGGAGACTGGAGTGACCATTGCCCCAAGGGCGCGTGCGGCCTG
CAGACCAAGATCCAGGGACCTAGAGGCCTCGGCGATGACACTGCGCTGAACGACGCGCGC
TTATTCTGCTGCCGCAGT**TGA**ACGGCGCCGCCGCCGCCGCTCTCTCCCGGGCCAGGAGGC
TAGTCCCACCTCTTGCTATTAAAGCTTCTCTGAGTTG

FIGURE 368

MERGAGAKLLPLLLLLRATGFTCAQTDGRNGYTAVIEVTSGGPWGDWAWPEMCPDGFFAS
GFSLKVEPPQGIPGDDTALNGIRLHCARGNVLGNTHVVESQSGSWGEWSEPLWCRGGAYL
VAFSLRVEAPTTLGDNTAANNVRFRCSDGEELQGPGLSWGDFGDWSDHCPKGACGLQTKI
QGPRGLGDDTALNDARLFCCRS

Important features of the protein:

Signal peptide:
1-24

Transmembrane domain:
None

N-myristoylation site:
41-47
89-95
156-162

Growth factor and cytokines receptors family signature 2:
103-110

FIGURE 369

GCCAACACTGGCCAAACCTCGGAGACCGTCCTGCGCTCTCTGGAGACGCGCTGTCCGCGC
CCAGGGTGGTGCC**ATG**TGGGGCGCTCGCCGCTCGTCCGTCTCCTCATCCTGGAACGCCGC
TTCGCTCCTGCAGCTGCTGCTGGCTGCGCTGCTGGCGGCGGGGGCGAGGGCCAGCGGCGA
GTACTGCCACGGCTGGCTGGACGCGCAGGGCGTCTGGCGCATCGGCTTCCAGTGTCCCGA
GCGCTTCGACGGCGGCGACGCCACCATCTGCTGCGGCAGCTGCGCGTTGCGCTACTGCTG
CTCCAGCGCCGAGGCGCGCCTGGACCAGGGCGGCTGCGACAATGACCGCCAGCAGGGCGC
TGGCGAGCCTGGCCGGGCGGACAAAGACGGCCCCGACGGCTCGGCAGTGCCCATCTACGT
GCCGTTCCTCATTGTTGGCTCCGTGTTTGTCGCCTTTATCATCTTGGGGTCCCTGGTGGC
AGCCTGTTGCTGCAGATGTCTCCGGCCTAAGCAGGATCCCCAGCAGAGCCGAGCCCCAGG
GGGTAACCGCTTGATGGAGACCATCCCCATGATCCCCAGTGCCAGCACCTCCCGGGGGTC
GTCCTCACGCCAGTCCAGCACAGCTGCCAGTTCCAGCTCCAGCGCCAACTCAGGGGCCCG
GGCGCCCCCAACAAGGTCACAGACCAACTGTTGCTTGCCGGAAGGGACCATGAACAACGT
GTATGTCAACATGCCCACGAATTTCTCTGTGCTGAACTGTCAGCAGGCCACCCAGATTGT
GCCACATCAAGGGCAGTATCTGCATCCCCCATACGTGGGGTACACGGTGCAGCACGACTC
TGTGCCCATGACAGCTGTGCCACCTTTCATGGACGGCCTGCAGCCTGGCTACAGGCAGAT
TCAGTCCCCCTTCCCTCACACCAACAGTGAACAGAAGATGTACCCAGCGGTGACTGTA**TA**
ACCGAGAGTCACTGGTGGGTTCCTTTACTGAAGGGAGACGAAGGCAGGGGTGGATTTTCG
AGGTGGAAGT

FIGURE 370

MWGARRSSVSSSWNAASLLQLLLAALLAAGARASGEYCHGWLDAQGVWRIGFQCPERFDG
GDATICCGSCALRYCCSSAEARLDQGGCDNDRQQGAGEPGRADKDGPDGSAVPIYVPFLI
VGSVFVAFIILGSLVAACCCRCLRPKQDPQQSRAPGGNRLMETIPMIPSASTSRGSSSRQ
SSTAASSSSSANSGARAPPTRSQTNCCLPEGTMNNVYVNMPTNFSVLNCQQATQIVPHQG
QYLHPPYVGYTVQHDSVPMTAVPPFMDGLQPGYRQIQSPFPHTNSEQKMYPAVTV

Important features of the protein:

Signal peptide:
1-33

Transmembrane domain:
54-78

N-glycosylation site:
223-226

cAMP- and cGMP-dependent protein kinase phosphorylation site:
5-8

N-myristoylation site:
3-8, 30-35, 60-65, 86-91, 132-137, 211-216, 268-273

Prokaryotic membrane lipoprotein lipid attachment site:
128-138

FIGURE 371

CACCAGACAGCACTCCAGCACTCTGTTTGGGGGGCATTCGAAACAGCAAAATCACTCATA
AAAGGCAAAAAATTGCAAAAAAAAAATAGTAATAACCAGCATGGCACTAAATAGACCATGA
AAAGACATGTGTGTGCAGTATGAAAATTGAGACAGGAAGGCAGAGTGTCAGCTTGTTCCA
CCTCAGCTGGGA**ATG**TGCATCAGGCAACTCAAGTTTTTCACCACGGCATGTGTCTGTGAA
TGTCCGCAAAACATTCTCTCTCCCCAGCCTTCATGTGTTAACCTGGGGATGATGTGGACC
TGGGCACTGTGGATGCTCCCTTCACTCTGCAAATTCAGCCTGGCAGCTCTGCCAGCTAAG
CCTGAGAACATTTCCTGTGTCTACTACTATAGGAAAAATTTAACCTGCACTTGGAGTCCA
GGAAAGGAAACCAGTTATACCCAGTACACAGTTAAGAGAACTTACGCTTTTGGAGAAAAA
CATGATAATTGTACAACCAATAGTTCTACAAGTGAAAATCGTGCTTCGTGCTCTTTTTTC
CTTCCAAGAATAACGATCCCAGATAATTATACCATTGAGGTGGAAGCTGAAAATGGAGAT
GGTGTAATTAAATCTCATATGACATACTGGAGATTAGAGAACATAGCGAAAACTGAACCA
CCTAAGATTTTCCGTGTGAAACCAGTTTTGGGCATCAAACGAATGATTCAAATTGAATGG
ATAAAGCCTGAGTTGGCGCCTGTTTCATCTGATTTAAAATACACACTTCGATTCAGGACA
GTCAACAGTACCAGCTGGATGGAAGTCAACTTCGCTAAGAACCGTAAGGATAAAAACCAA
ACGTACAACCTCACGGGGCTGCAGCCTTTTACAGAATATGTCATAGCTCTGCGATGTGCG
GTCAAGGAGTCAAAGTTCTGGAGTGACTGGAGCCAAGAAAAAATGGGAATGACTGAGGAA
GAAGCTCCATGTGGCCTGGAACTGTGGAGAGTCCTGAAACCAGCTGAGGCGGATGGAAGA
AGGCCAGTGCGGTTGTTATGGAAGAAGGCAAGAGGAGCCCCAGTCCTAGAGAAAACACTT
GGCTACAACATATGGTACTATCCAGAAAGCAACACTAACCTCACAGAAACAATGAACACT
ACTAACCAGCAGCTTGAACTGCATCTGGGAGGCGAGAGCTTTTGGGTGTCTATGATTTCT
TATAATTCTCTTGGGAAGTCTCCAGTGGCCACCCTGAGGATTCCAGCTATTCAAGAAAAA
TCATTTCAGTGCATTGAGGTCATGCAGGCCTGCGTTGCTGAGGACCAGCTAGTGGTGAAG
TGGCAAAGCTCTGCTCTAGACGTGAACACTTGGATGATTGAATGGTTTCCGGATGTGGAC
TCAGAGCCCACCACCCTTTCCTGGGAATCTGTGTCTCAGGCCACGAACTGGACGATCCAG
CAAGATAAATTAAAACCTTTCTGGTGCTATAACATCTCTGTGTATCCAATGTTGCATGAC
AAAGTTGGCGAGCCATATTCCATCCAGGCTTATGCCAAAGAAGGCGTTCCATCAGAAGGT
CCTGAGACCAAGGTGGAGAACATTGGCGTGAAGACGGTCACGATCACATGGAAAGAGATT
CCCAAGAGTGAGAGAAAGGGTATCATCTGCAACTACACCATCTTTTACCAAGCTGAAGGT
GGAAAAGGATTCTGTAAGCACGCCCATAGCGAAGTGGAAAAAAACCCCAAGCCCCAGATA
GATGCTATGGATAGACCTGTTGTAGGCATGGCTCCCCCATCTCATTGTGACTTGCAACCT
GGCATGAATCACTTAGCTTCTTTAAATCTCTCTGAAAATGGGGCCAAGAGCACCCACCTT
TTGGGGTTTTGGGGGTTAAATGAGAGTGAAGTGACAGTACCTGAGAGGAGAGTCCTGAGG
AAATGGAAGGAGTTGTTA**TAA**TTTGTCCTGGTTAGGCCCTGAATTGACCTCCCGGGAGCT
CCCCGACCATCATTCCCAGGAATGGCGTGCCTGGCTTAAAGAGTGAGGAGGAACAGACCC
TGTCACCATGACTTCTACTGCCCCTGCCAAATCATGCTTTTGTTTTTCAGTCCACCTTAT
CTCCTGACATCTTAAATACTGGGCAAGGCTTGGATTCTTGCTTAGGCTAAATAATTTTTT
CTTATGGTAAAATACACGTAAAATATTTTTCCAGTTTAAACATTTGAAAGTGTACAATTT
AGTGGCATTAGAAGCATTCACAATATTGTGCAACCATCACCACTATTTCCAGAACTCTTC
TATTTCTGCCCAAATAGAAGCCCTATACCCATTCATTAGTCACTCCCCATTCCTCTCCTC
CCACAGCCCCTGGCAACTACCAAACTGCTTTGTGTCTCTATGGATTGCCTATTTTGGATA
TTTCATATACATAGAATCATAAANTAAAAAAAAAAAAAAAAAAA

FIGURE 372

MCIRQLKFFTTACVCECPQNILSPQPSCVNLGMMWTWALWMLPSLCKFSLAALPAKPENI
SCVYYYRKNLTCTWSPGKETSYTQYTVKRTYAFGEKHDNCTTNSSTSENRASCSFFLPRI
TIPDNYTIEVEAENGDGVIKSHMTYWRLENIAKTEPPKIFRVKPVLGIKRMIQIEWIKPE
LAPVSSDLKYTLRFRTVNSTSWMEVNFAKNRKDKNQTYNLTGLQPFTEYVIALRCAVKES
KFWSDWSQEKMGMTEEEAPCGLELWRVLKPAEADGRRPVRLLWKKARGAPVLEKTLGYNI
WYYPESNTNLTETMNTTNQQLELHLGGESFWVSMISYNSLGKSPVATLRIPAIQEKSFQC
IEVMQACVAEDQLVVKWQSSALDVNTWMIEWFPDVDSEPTTLSWESVSQATNWTIQQDKL
KPFWCYNISVYPMLHDKVGEPYSIQAYAKEGVPSEGPETKVENIGVKTVTITWKEIPKSE
RKGIICNYTIFYQAEGGKGFCKHAHSEVEKNPKPQIDAMDRPVVGMAPPSHCDLQPGMNH
LASLNLSENGAKSTHLLGFWGLNESEVTVPERRVLRKWKELL

Important features of the protein:

Signal peptide:
1-46

Transmembrane domain:
None

N-glycosylation site:
59-63, 69-73, 99-103, 103-107, 125-129, 198-202, 215-219, 219-223, 309-313, 315-319, 412-416, 427-431, 487-491, 545-549, 563-567

N-myristoylation site:
32-38, 137-143, 483-489, 550-556, 561-567

Amidation site:
274-278

Growth factor and cytokines receptors family signature 1:
62-75

Fibronectin type III domain:
54-144
154-247

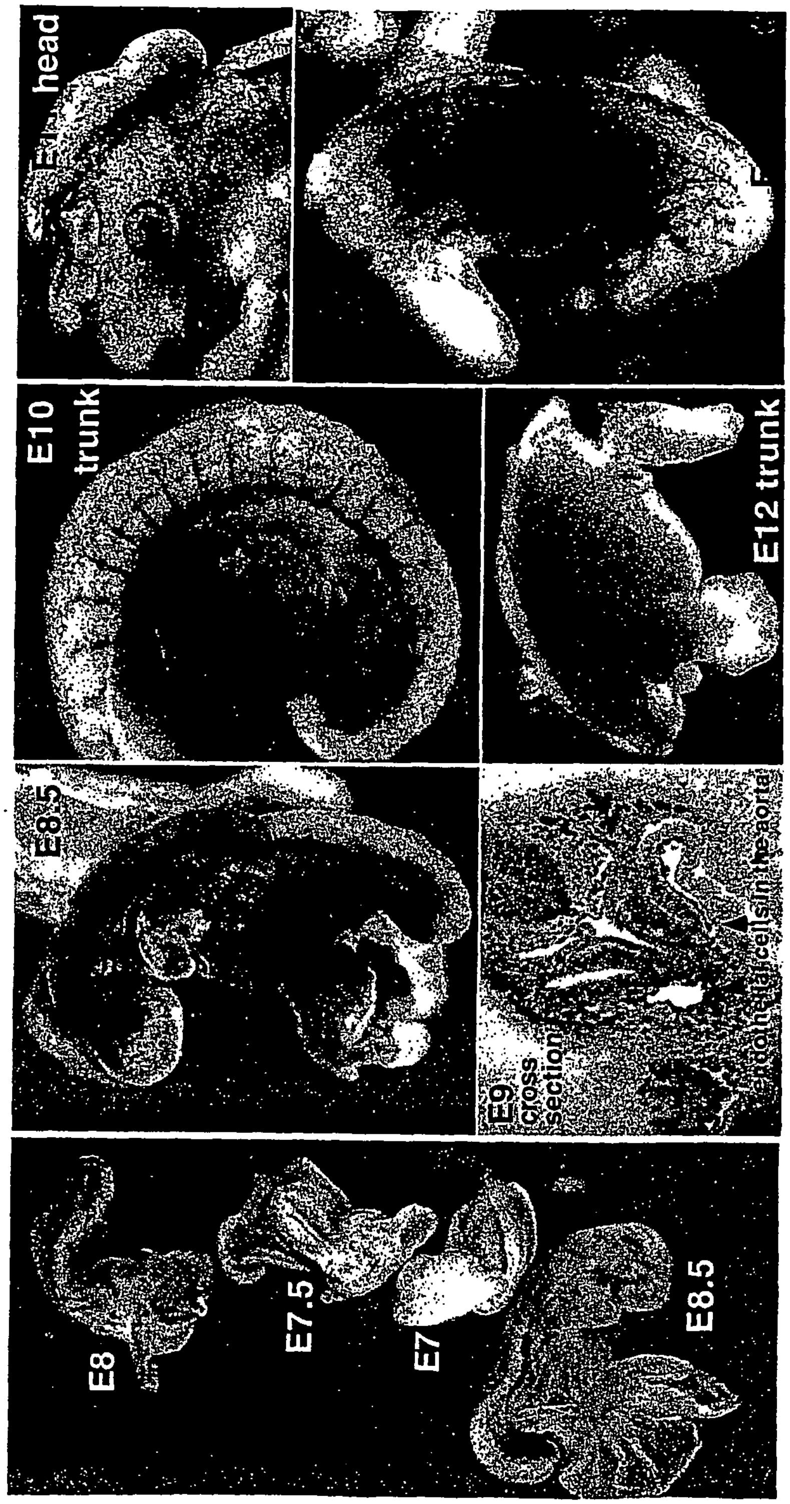
FIGURE 373

CCAGGTCCAACTGCACCTCGGTTCTATCGATTGAATTCCCCGGGGATCCTCTAGAGATCC
CTCGACCTCGACCCACGCGTCCGCCAAGCTGGCCCTGCACGGCTGCAAGGGAGGCTCCTG
TGGACAGGCCAGGCAGGTGGGCCTCAGGAGGTGCCTCCAGGCGGCCAGTGGGCCTGAGGC
CCCAGCAAGGGCTAGGGTCCATCTCCAGTCCCAGGACACAGCAGCGGCCACCATGGCCAC
GCCTGGGCTCCAGCAGCATCAGCAGCCCCCAGGACCGGGGGAGGCACAGGTGGCCCCCAC
CACCCGGAGGAGCAGCTCCTGCCCCTGTCCGGGGG<u>**ATG**</u>ACTGATTCTCCTCCGCCAGGCC
ACCCAGAGGAGAAGGCCACCCCGCCTGGAGGCACAGGCCATGAGGGGCTCTCAGGAGGTG
CTGCTGATGTGGCTTCTGGTGTTGGCAGTGGGCGGCACAGAGCACGCCTACCGGCCCGGC
CGTTAGGGTGTGTGCTGTCCCGGGCTCACGGGGACCCTGTCTCCGAGTCGTTCGTGCAGC
GTGTGTACCAGCCCTTCCTCACCACCTGCGACGGGCACCGGGCCTGCAGCACCTACCGAA
CCATTTATAGGACCGCCTACCGCCGCAGCCCTGGGCTGGCCCCTGCCAGGCCTCGCTACG
CGTGCTGCCCCGGCTGGAAGAGGACCAGCGGGCTTCCTGGGGCCTGTGGAGCAGCAATAT
GCCAGCCGCCATGCCGGAACGGAGGGAGCTGTGTCCAGCCTGGCCGCTGCCGCTGCCCTG
CAGGATGGCGGGGTGACACTTGCCAGTCAGATGTGGATGAATGCAGTGCTAGGAGGGGCG
GCTGTCCCCAGCGCTGCATCAACACCGCCGGCAGTTACTGGTGCCAGTGTTGGGAGGGGC
ACAGCCTGTCTGCAGACGGTACACTCTGTGTGCCCAAGGGAGGGCCCCCCAGGGTGGCCC
CCAACCCGACAGGAGTGGACAGTGCAATGAAGGAAGAAGTGCAGAGGCTGCAGTCCAGGG
TGGACCTGCTGGAGGAGAAGCTGCAGCTGGTGCTGGCCCCACTGCACAGCCTGGCCTCGC
AGGCACTGGAGCATGGGCTCCCGGACCCCGGCAGCCTCCTGGTGCACTCCTTCCAGCAGC
TCGGCCGCATCGACTCCCTGAGCGAGCAGATTTCCTTCCTGGAGGAGCAGCTGGGGTCCT
GCTCCTGCAAGAAAGACTCG<u>**TGA**</u>CTGCCCAGCGCCCCAGGCTGGACTGAGCCCCTCACGC
CGCCCTGCAGCCCCCATGCCCCTGCCCAACATGCTGGGGGTCCAGAAGCCACCTCGGGGT
GACTGAGCGGAAGGCCAGGCAGGGCCTTCCTCCTTTTCCTCCTCCCCTTCCCTCGGGAGG
GTCCCCAGACCCTGGCATGGGATGGGCTGGGATTTTTTTTGTGAATCCACCCCTGGCTAC
CCCCACCCTGGTTACCCCAACGGCATCCCAAGGCCAGGTGGGCCCTCAGCTGAGGGAAGG
TACGAGTTCCCCTGCTGGAGCCTGGGACCCATGGCACAGGCCAGGCAGCCCGGAGGCTGG
GTGGGGCCTCAGTGGGGGCTGCTGCCTGACCCCCAGCACAATAAAAATGAAACGTGAAAA
AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGGGCGGCCGCGACTCTAGAGTC
GACCTGCAGAAGCTTGGCCGCCATGGCCCAACTTGTTTATTGCAGCTTATAATGGTTACAAT

FIGURE 374

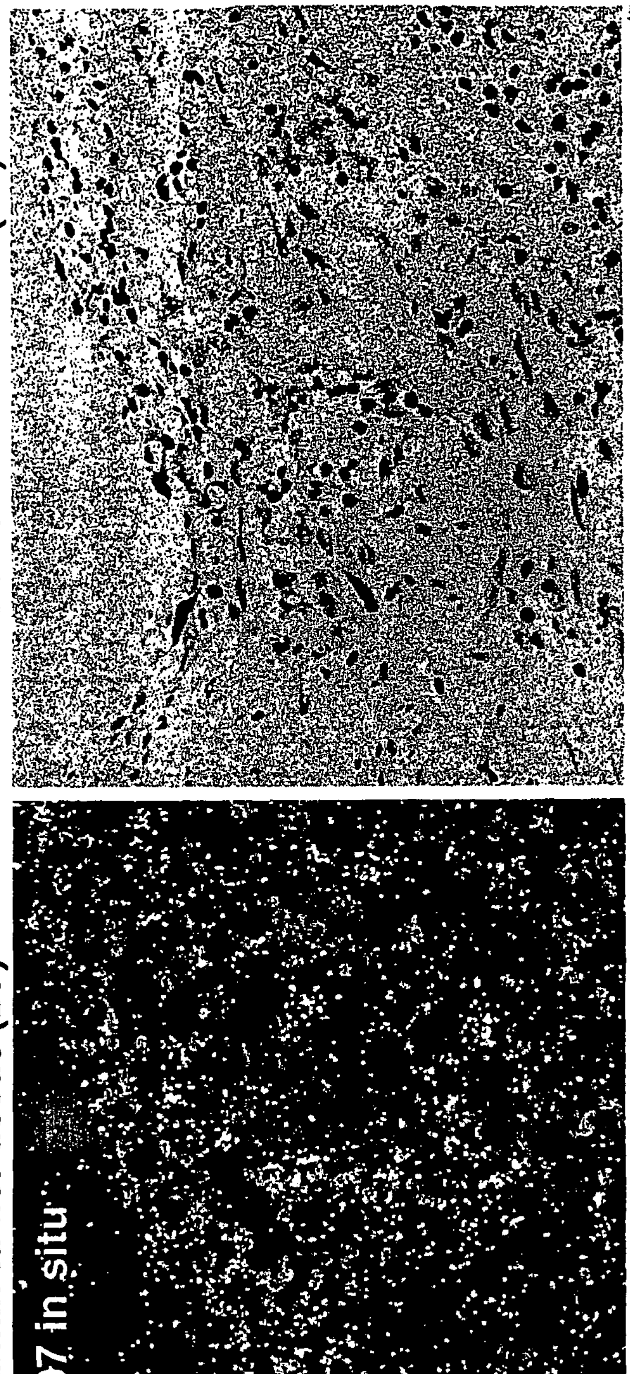
MTDSPPPGHPEEKATPPGGTGHEGLSGGAADVASGVGSGRHRARLPARPLGCVLSRAHGD
PVSESFVQRVYQPFLTTCDGHRACSTYRTIYRTAYRRSPGLAPARPRYACCPGWKRTSGL
PGACGAAICQPPCRNGGSCVQPGRCRCPAGWRGDTCQSDVDECSARRGGCPQRCINTAGS
YWCQCWEGHSLSADGTLCVPKGGPPRVAPNPTGVDSAMKEEVQRLQSRVDLLEEKLQLVL
APLHSLASQALEHGLPDPGSLLVHSFQQLGRIDSLSEQISFLEEQLGSCSCKKDS

FIGURE 375



Wholemount In Situ with PRO1449 Orthologue

FIGURE 376



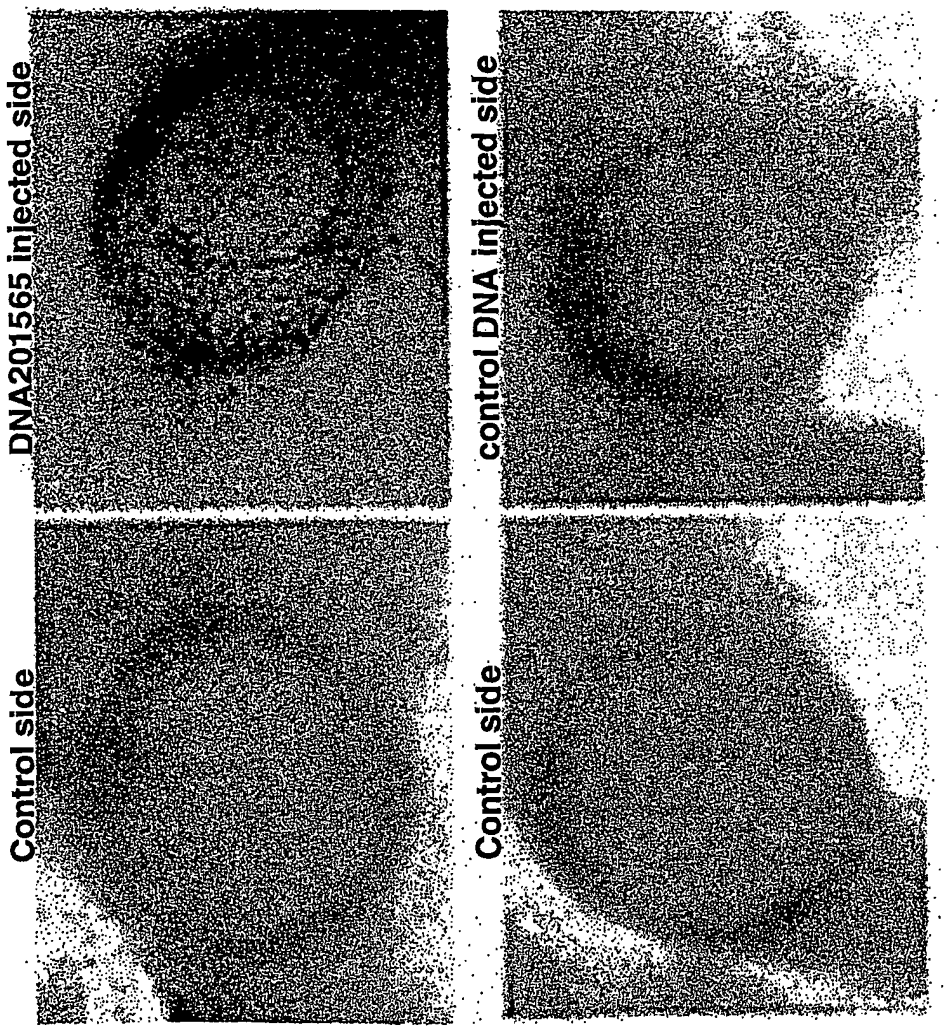
Human tumor tissue (BF)

Human tumor tissue (DF)

PRO1449 is expressed in vasculature of many inflamed and diseased tissues

FIGURE 377

Mouse orthologue of PRO1449 induces ectopic vessels in the eyes of chicken embryos



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60/220,664	25 July 2000 (25.07.2000)	US
PCT/US00/20710	28 July 2000 (28.07.2000)	US
60/222,695	2 August 2000 (02.08.2000)	US
09/643,657	17 August 2000 (17.08.2000)	US
PCT/US00/23522	23 August 2000 (23.08.2000)	US
PCT/US00/23328	24 August 2000 (24.08.2000)	US
60/230,978	7 September 2000 (07.09.2000)	US
60/000,000	15 September 2000 (15.09.2000)	US
09/664,610	18 September 2000 (18.09.2000)	US
09/665,350	18 September 2000 (18.09.2000)	US
60/242,922	24 October 2000 (24.10.2000)	US
09/709,238	8 November 2000 (08.11.2000)	US
PCT/US00/30952	8 November 2000 (08.11.2000)	US
PCT/US00/30873	10 November 2000 (10.11.2000)	US
PCT/US00/32678	1 December 2000 (01.12.2000)	US
09/747,259	20 December 2000 (20.12.2000)	US
PCT/US00/34956	20 December 2000 (20.12.2000)	US
09/767,609	22 January 2001 (22.01.2001)	US
09/796,498	28 February 2001 (28.02.2001)	US
PCT/US01/06520	28 February 2001 (28.02.2001)	US
PCT/US01/06666	1 March 2001 (01.03.2001)	US
09/802,706	9 March 2001 (09.03.2001)	US
09/808,689	14 March 2001 (14.03.2001)	US
09/816,744	22 March 2001 (22.03.2001)	US
09/828,366	5 April 2001 (05.04.2001)	US
09/854,208	10 May 2001 (10.05.2001)	US
09/854,280	10 May 2001 (10.05.2001)	US
09/866,028	25 May 2001 (25.05.2001)	US
09/866,034	25 May 2001 (25.05.2001)	US
PCT/US01/17092	25 May 2001 (25.05.2001)	US
09/870,574	30 May 2001 (30.05.2001)	US
PCT/US01/17443	30 May 2001 (30.05.2001)	US
PCT/US01/17800	1 June 2001 (01.06.2001)	US

(71) Applicant *(for all designated States except US)*: **GENENTECH, INC.** [US/US]; 1 DNA Way, South San Francisco, CA 94080-4990 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BAKER, Kévin, P.** [GB/US]; 14006 Indian Run Drive, Darnestown, MD 20878 (US). **FERRARA, Napoleone** [US/US]; #704, 2090 Pacific Avenue, San Francisco, CA 94109 (US). **GERBER, Hanspeter** [CH/US]; #5, 1121 Tennessee Street, San Francisco, CA 94107 (US). **GERRITSEN, Mary, E.** [CA/US]; 541 Parrott Drive, San Mateo, CA 94402 (US). **GODDARD, Audrey** [CA/US]; 110 Congo Street, San Francisco, CA 94131 (US). **GODOWSKI, Paul, J.** [US/US]; 25 Orange Court, Hillsborough, CA 94010 (US). **GURNEY, Austin, L.** [US/US]; 1 Debbie Lane, Belmont, CA 94002 (US). **HILLAN, Kenneth, J.** [GB/US]; 64 Seward Street, San Francisco, CA 94114 (US). **MARSTERS, Scot, A.** [US/US]; 990 Cherry Street, San Carlos, CA 94070 (US). **PAN, James** [CA/US]; 2705 Coronet Boulevard, Belmont, CA 94002 (US). **PAONI, Nicholas, F.** [US/US]; 1756 Terrace Drive, Belmont, CA 94002 (US). **STEPHAN, Jean-Philippe, F.** [FR/US]; 320 C Lansdale Avenue, Millbrae, CA 94030 (US). **WATANABE, Colin, K.** [US/US]; 128 Corliss Drive, Moraga, CA 94556 (US). **WILLIAMS, P., Mickey** [US/US]; 509 Alto Avenue, Half Moon Bay, CA 94019 (US). **WOOD, William, I.** [US/US]; 35 Southdown Court, Hillsborough, CA 94010 (US). **YE, Weilan** [CN/US]; 119 Barkentine Street, Foster City, CA 94404 (US).

[Continued on next page]

(54) Title: COMPOSITIONS AND METHODS FOR THE DIAGNOSIS AND TREATMENT OF DISORDERS INVOLVING ANGIOGENESIS

(57) Abstract: Compositions and methods are disclosed for stimulating or inhibiting angiogenesis and/or cardiovascularization in mammals, including humans. Pharmaceutical compositions are based on polypeptides or antagonists thereto that have been identified for one or more of these uses. Disorders that can be diagnosed, prevented, or treated by the compositions herein include trauma such as wounds, various cancers, and disorders of the vessels including atherosclerosis and cardiac hypertrophy.In addition, the present invention is directed to novel polypeptides and to nucleic acid molecules encoding those polypeptides. Also provided herein are vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide molecules comprising the polypeptides of the present invention fused to heterologous polypeptide sequences, antibodies which bind to the polypeptides of the present invention and to methods for producing the polypeptides of the present invention.

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(74) **Agents:** **AGARWAL, Atulya, R.** et al.; c/o GENENTECH, INC., MS49, 1 DNA Way, South San Francisco, CA 94080-4990 (US).

(81) **Designated States** *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C07K14/47 A61K38/17 C07K16/18

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,L	WO 99 46281 A (BAKER KEVIN P ;CHEN JIAN (US); GENENTECH INC (US); GURNEY AUSTIN () 16 September 1999 (1999-09-16) see PRO181	1-19
X,L	US 5 968 744 A (CORLEY NEIL C ET AL) 19 October 1999 (1999-10-19) L: priority. the whole document	1-19
X	WO 99 50405 A (GENETICS INST) 7 October 1999 (1999-10-07) see pk65_4 and seq.ID's 11 and 12	1-19
X	WO 99 43802 A (KATO SEISHI ;KIMURA TOMOKO (JP); PROTEGENE INC (JP); SEKINE SHINGO) 2 September 1999 (1999-09-02) see clone HP02239.	1-19

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 August 2002	29. 11. 2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Smalt, R

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 10363 A (WEI YING FEI ;HUMAN GENOME SCIENCES INC (US); ROSEN CRAIG A (US);) 4 March 1999 (1999-03-04) see secreted protein 24	1-19
X	WO 99 33979 A (CHIRON CORP) 8 July 1999 (1999-07-08) the whole document	1-19
A	WO 95 29242 A (CHILDRENS MEDICAL CENTER) 2 November 1995 (1995-11-02) the whole document	
A	EP 0 335 243 A (HARVARD COLLEGE) 4 October 1989 (1989-10-04) the whole document	
A	FOLKMAN J: "CLINICAL APPLICATIONS OF RESEARCH ON ANGIOGENESIS" NEW ENGLAND JOURNAL OF MEDICINE, THE, MASSACHUSETTS MEDICAL SOCIETY, WALTHAM, MA, US, vol. 333, no. 26, 28 December 1995 (1995-12-28), pages 1757-1763, XP000654557 ISSN: 0028-4793 the whole document	
A	KLAGSBRUN M: "REGULATORS OF ANGIOGENESIS: STIMULATORS, INHIBITORS, AND EXTRACELLULAR MATRIX" JOURNAL OF CELLULAR BIOCHEMISTRY, LISS, NEW YORK, NY, US, vol. 47, no. 3, 1 November 1991 (1991-11-01), pages 199-200, XP000616588 ISSN: 0730-2312 the whole document	
P,X, L	WO 00 53756 A (BOTSTEIN DAVID;BAKER KEVIN P ; GENENTECH INC (US); ASHKENAZI AVI J) 14 September 2000 (2000-09-14) see seq.ID.322; L: priority.	1-19
P,X, L	WO 00 53751 A (BAKER KEVIN P ;GENENTECH INC (US); NAPIER MARY A (US); ASHKENAZI A) 14 September 2000 (2000-09-14) the whole document	1-21,23, 27-29, 31,32, 34,35
P,X	WO 01 00828 A (CORIXA CORP ;FANGER GARY R (US); RETTER MARC W (US); WANG TONGTONG) 4 January 2001 (2001-01-04) see seq.ID.327	1-21,23, 27-29, 31,32, 34,35

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E,L	WO 02 08284 A (FERRARA NAPOLEONE ;STEPHAN JEAN PHILIPPE F (US); WILLIAMS P MICKEY) 31 January 2002 (2002-01-31) See seq.ID's 1 and 120. L: priority. -----	1-35,37, 41

International application No.
PCT/US 01/19692

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 20-34, 37 and 41 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-35, 37, 41 all partially

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 20-28,31,34,35,37, and 41 relate to products defined by reference to a desirable characteristic or property, namely having (ant)agonistic activity towards the protein(s) of claim 1.
The application provides no support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for any such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search impossible. Consequently, the search of said claims, in as far as the (ant)agonists are concerned, has been carried out for those aspects which appear to be clear, supported and disclosed, namely those parts relating to antibodies directed against the protein(s) of claiml.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: 1-35, 37, 41 all partially

Nucleic acid with at least 80% identity to seq.ID.1 and protein encoded thereby, vector, host cell, method for producing the protein, chimeric protein, antibody, and pharmaceutical compositions.

Inventions 2-187: 1-42, all partially,
and as far as applicable

Subject matter as defined for invention 1 above, but limited to the respective nucleic acid sequences 3-373 (odd numbers) and the polypeptides encoded thereby (seq.ID's 4-374, even numbers).

For the sake of conciseness, the first subject matter is explicitly defined, the other subject matters are defined by analogy thereto.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/19692

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 9946281	A	16-09-1999	US	6391311	B1	21-05-2002
			AU	3072199	A	27-09-1999
			CA	2321677	A1	16-09-1999
			US	2002127584	A1	12-09-2002
			US	2002094416	A1	18-07-2002
			WO	9946281	A2	16-09-1999
			US	2002156006	A1	24-10-2002
			US	2002169284	A1	14-11-2002
			ZA	9901937	A	17-04-2000
			EP	1241187	A2	18-09-2002
			AU	3075099	A	11-10-1999
			CA	2322792	A1	23-09-1999
			EP	1064382	A2	03-01-2001
			WO	9947677	A2	23-09-1999
			US	6455283	B1	24-09-2002
			EP	1241183	A2	18-09-2002
			US	2002072496	A1	13-06-2002
			US	2002142961	A1	03-10-2002
			US	2002072067	A1	13-06-2002
			US	2002072092	A1	13-06-2002
			US	2002072497	A1	13-06-2002
			US	2002103125	A1	01-08-2002
			US	2002123463	A1	05-09-2002
			US	2002132252	A1	19-09-2002
			US	2002127576	A1	12-09-2002
			US	2002132253	A1	19-09-2002
			US	2002160384	A1	31-10-2002
			AU	735081	B2	28-06-2001
			AU	1532499	A	15-06-1999
			CA	2309358	A1	03-06-1999
			EP	1241180	A2	18-09-2002
			EP	1032667	A2	06-09-2000
			WO	9927098	A2	03-06-1999
			US	6410708	B1	25-06-2002
			EP	1241185	A2	18-09-2002
			EP	1249491	A2	16-10-2002
			EP	1251139	A2	23-10-2002
			US	2002161199	A1	31-10-2002
			EP	1241179	A2	18-09-2002
			EP	1241186	A2	18-09-2002
			AU	741133	B2	22-11-2001
			AU	3757099	A	08-11-1999
			CA	2324297	A1	28-10-1999
			EP	1071773	A1	31-01-2001
			JP	2002512032	T	23-04-2002
			WO	9954467	A1	28-10-1999
			US	2002147322	A1	10-10-2002
			EP	1241251	A2	18-09-2002
			US	2002119118	A1	29-08-2002
US 5968744	A	19-10-1999	US	2002103342	A1	01-08-2002
			US	6348576	B1	19-02-2002
WO 9950405	A	07-10-1999	AU	3457299	A	18-10-1999
			CA	2324492	A1	07-10-1999
			EP	1068307	A1	17-01-2001
			JP	2002509722	T	02-04-2002
			WO	9950405	A1	07-10-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/19692

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 9943802	A	02-09-1999	AU	2549399	A	15-09-1999
			CA	2322711	A1	02-09-1999
			EP	1056847	A2	06-12-2000
			WO	9943802	A2	02-09-1999
			JP	2002506615	T	05-03-2002
WO 9910363	A	04-03-1999	AU	8921598	A	16-03-1999
			CA	2302387	A1	04-03-1999
			EP	1017707	A1	12-07-2000
			JP	2002532054	T	02-10-2002
			WO	9910363	A1	04-03-1999
			US	6410709	B1	25-06-2002
			US	2001016647	A1	23-08-2001
WO 9933979	A	08-07-1999	AU	1929599	A	19-07-1999
			EP	1042470	A2	11-10-2000
			JP	2002511231	T	16-04-2002
			WO	9933979	A2	08-07-1999
			US	2002034800	A1	21-03-2002
WO 9529242	A	02-11-1995	US	5639725	A	17-06-1997
			US	5792845	A	11-08-1998
			AU	692865	B2	18-06-1998
			AU	2461795	A	16-11-1995
			BR	9507479	A	16-09-1997
			CA	2188813	A1	02-11-1995
			CN	1149319	A	07-05-1997
			CZ	9603122	A3	14-05-1997
			EP	0758390	A1	19-02-1997
			HU	76095	A2	30-06-1997
			JP	9512173	T	09-12-1997
			NZ	285501	A	26-02-1998
			WO	9529242	A1	02-11-1995
			US	5885795	A	23-03-1999
			US	5733876	A	31-03-1998
			US	5776704	A	07-07-1998
			ZA	9503419	A	11-01-1996
EP 0335243	A	04-10-1989	US	4900673	A	13-02-1990
			AT	96844	T	15-11-1993
			AU	621358	B2	12-03-1992
			AU	3433189	A	16-10-1989
			CA	1331356	A1	09-08-1994
			DE	68910354	D1	09-12-1993
			DE	68910354	T2	03-03-1994
			DK	233390	A	26-11-1990
			EP	0335243	A2	04-10-1989
			IE	890954	L	28-09-1989
			JP	3503641	T	15-08-1991
			PT	90129	A	10-11-1989
			WO	8909277	A1	05-10-1989
			ZA	8902270	A	24-12-1991
WO 0053756	A	14-09-2000	AU	1748200	A	19-06-2000
			AU	1749900	A	12-07-2000
			AU	2192800	A	12-07-2000
			AU	2224800	A	28-09-2000
			AU	2399300	A	28-09-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/19692

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0053756 A		AU 2495200 A	28-09-2000
		AU 2596700 A	28-09-2000
		AU 2600800 A	28-09-2000
		AU 2879400 A	31-07-2001
		AU 2883600 A	28-09-2000
		AU 3072199 A	27-09-1999
		AU 3107700 A	28-09-2000
		AU 3381600 A	28-09-2000
		AU 3514400 A	28-09-2000
		CA 2321677 A1	16-09-1999
		EP 1173563 A1	23-01-2002
		EP 1159419 A1	05-12-2001
		EP 1220905 A2	10-07-2002
		EP 1135485 A2	26-09-2001
		EP 1141284 A2	10-10-2001
		EP 1159422 A1	05-12-2001
		EP 1141289 A2	10-10-2001
		US 2002119130 A1	29-08-2002
		WO 0053753 A2	14-09-2000
		WO 0053754 A1	14-09-2000
		WO 0053755 A2	14-09-2000
		WO 0153486 A1	26-07-2001
		WO 0053756 A2	14-09-2000
		WO 0053757 A2	14-09-2000
		WO 0053758 A2	14-09-2000
		US 2002127584 A1	12-09-2002
		US 2002094416 A1	18-07-2002
		WO 0032221 A2	08-06-2000
		WO 0053750 A1	14-09-2000
		WO 0037638 A2	29-06-2000
		WO 0037640 A2	29-06-2000
		WO 0053751 A1	14-09-2000
		WO 0053752 A2	14-09-2000
		US 2002119118 A1	29-08-2002
		US 2002161199 A1	31-10-2002
		US 2002156006 A1	24-10-2002
		US 2002169284 A1	14-11-2002
		US 2002072496 A1	13-06-2002
		US 2002142961 A1	03-10-2002
		US 2002072067 A1	13-06-2002
		US 2002072092 A1	13-06-2002
		US 2002072497 A1	13-06-2002
		US 2002103125 A1	01-08-2002
WO 0053751 A	14-09-2000	AU 1748200 A	19-06-2000
		AU 1749900 A	12-07-2000
		AU 2192800 A	12-07-2000
		AU 2224800 A	28-09-2000
		AU 2399300 A	28-09-2000
		AU 2495200 A	28-09-2000
		AU 2596700 A	28-09-2000
		AU 2600800 A	28-09-2000
		AU 2879400 A	31-07-2001
		AU 2883600 A	28-09-2000
		AU 3072199 A	27-09-1999
		AU 3107700 A	28-09-2000
		AU 3381600 A	28-09-2000
		AU 3514400 A	28-09-2000

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No
PCT/US 01/19692

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 0053751	A		CA	2321677	A1	16-09-1999
			EP	1173563	A1	23-01-2002
			EP	1159419	A1	05-12-2001
			EP	1220905	A2	10-07-2002
			EP	1135485	A2	26-09-2001
			EP	1141284	A2	10-10-2001
			EP	1159422	A1	05-12-2001
			EP	1141289	A2	10-10-2001
			US	2002119130	A1	29-08-2002
			WO	0053753	A2	14-09-2000
			WO	0053754	A1	14-09-2000
			WO	0053755	A2	14-09-2000
			WO	0153486	A1	26-07-2001
			WO	0053756	A2	14-09-2000
			WO	0053757	A2	14-09-2000
			WO	0053758	A2	14-09-2000
			US	2002127584	A1	12-09-2002
			US	2002094416	A1	18-07-2002
			WO	0032221	A2	08-06-2000
			WO	0053750	A1	14-09-2000
			WO	0037638	A2	29-06-2000
			WO	0037640	A2	29-06-2000
			WO	0053751	A1	14-09-2000
			WO	0053752	A2	14-09-2000
			US	2002119118	A1	29-08-2002
			US	2002161199	A1	31-10-2002
			US	2002156006	A1	24-10-2002
			US	2002169284	A1	14-11-2002
			US	2002072496	A1	13-06-2002
			US	2002142961	A1	03-10-2002
			US	2002072067	A1	13-06-2002
			US	2002072092	A1	13-06-2002
			US	2002072497	A1	13-06-2002
			US	2002103125	A1	01-08-2002
WO 0100828	A	04-01-2001	AU	5902700	A	31-01-2001
			BR	0012069	A	27-08-2002
			CN	1367829	T	04-09-2002
			EP	1196565	A2	17-04-2002
			HU	0201757	A2	28-09-2002
			NO	20016427	A	25-02-2002
			WO	0100828	A2	04-01-2001
			US	2002168637	A1	14-11-2002
			TR	200200691	T2	21-10-2002
WO 0208284	A	31-01-2002	US	2002042367	A1	11-04-2002
			US	2002010137	A1	24-01-2002
			US	2002106743	A1	08-08-2002
			US	2002052027	A1	02-05-2002
			US	2002058309	A1	16-05-2002
			US	2002102723	A1	01-08-2002
			AU	6531101	A	17-12-2001
			AU	7197301	A	05-02-2002
			AU	7315001	A	30-01-2002
			AU	7885201	A	08-01-2002
			WO	0193983	A1	13-12-2001
			WO	0200690	A2	03-01-2002
			WO	0208288	A2	31-01-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/19692

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0208284 A		WO 0208284 A2	31-01-2002
		AU 1916701 A	16-07-2001
		AU 2055401 A	12-06-2001
		AU 6391000 A	19-02-2001
		AU 6802801 A	24-09-2001
		AU 6901800 A	12-06-2001
		EP 1244784 A2	02-10-2002
		EP 1250426 A2	23-10-2002
		WO 0140464 A1	07-06-2001
		WO 0149715 A2	12-07-2001
		WO 0140466 A2	07-06-2001
		WO 0168848 A2	20-09-2001
		US 2002127584 A1	12-09-2002
		US 2002094416 A1	18-07-2002
		US 2002160374 A1	31-10-2002
		US 2002146709 A1	10-10-2002
		US 2002132240 A1	19-09-2002
		US 2002142958 A1	03-10-2002
		US 2002150976 A1	17-10-2002
		US 2002132981 A1	19-09-2002
		US 2002165143 A1	07-11-2002
		US 2002156004 A1	24-10-2002
		US 2002142419 A1	03-10-2002
		US 2002102647 A1	01-08-2002
		US 2002110859 A1	15-08-2002
		US 2002142959 A1	03-10-2002
		US 2002115145 A1	22-08-2002
		US 2002132768 A1	19-09-2002
		US 2002127643 A1	12-09-2002
		US 2002156006 A1	24-10-2002
		US 2002169284 A1	14-11-2002
		US 2002072496 A1	13-06-2002
		US 2002142961 A1	03-10-2002
		US 2002072067 A1	13-06-2002
		US 2002072092 A1	13-06-2002
		US 2002072497 A1	13-06-2002
		US 2002103125 A1	01-08-2002